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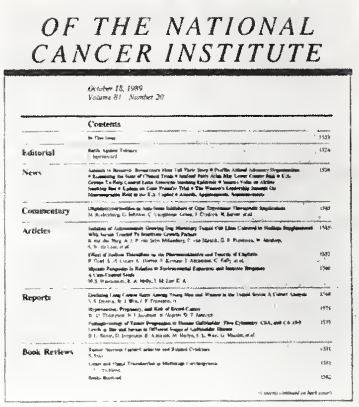
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Contents

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National Institutes of Health Consensus Development Conference on Oral Complications of Cancer Therapies: Diagnosis, Prevention, and Treatment

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April 17–19, 1989

TABLE OF CONTENTS

Page

IV. Management of Acute Problems

V. Management of Chronic Problems

Introduction

Philip C. Fox

Of the 1 million Americans who are diagnosed with cancer each year, approximately 400,000 will develop oral complications from their cancer treatments. The oral tissues may be affected by all forms of cancer therapy, including radiation treatments to the head and neck region, cytotoxic chemotherapy, bone marrow transplantation, and oral-maxillofacial surgery. Complications may be acute or chronic. The most common oral complications that arise during cancer treatment are mucosal inflammation, ulceration, bleeding, fungal, bacterial, and viral infections, dental or periodontal infections, and salivary gland dysfunction. These often are painful and difficult to treat and diminish the quality of life for patients at a particularly vulnerable time. Oral complications frequently interfere with chemosensory function and alimentation, affecting the nutritional status of patients. They may become so severe as to cause problems of compliance and discourage patients from continuing necessary cancer treatment. Research has demonstrated that during cancer treatment, the oral cavity may serve as a portal of entry for acute life-threatening or fatal systemic infections.

Chronic oral complications also accompany all forms of cancer therapy. Conditions include osteoradionecrosis, salivary gland dysfunction, second malignancies, growth and developmental abnormalities of hard and soft tissues of the head and neck, and taste disturbances. These complications take on added significance as treatments increase in intensity (often with a concomitant increase in severity of side effects) and as greater numbers of individuals survive their cancers for longer times.

The management of oral complications has been a major issue for both clinicians and researchers as new cancer treatments have evolved in the last 20 years. More recently, there has been increasing emphasis on means of preventing or minimizing these complications. Investigators have shown that pretherapy interventions may have a significant impact on both the incidence and severity of certain oral side effects. It was thought to be timely to review the literature in this important area and arrive at a consensus on the optimal strategies for patient management. With these purposes in mind, a National Institutes of Health Consensus Development Conference was organized on "Oral Complications of Cancer Therapies: Diagnosis, Prevention, and Treatment" and was held April 17–19, 1989, in Bethesda, MD. Investigators reviewed the literature and presented new data on all aspects of oral complications of cancer treatments. The articles in this volume were prepared by the speakers from their presentations. Based on the data presented and public comments by conference attendees, the Consensus Panel answered several key questions about the utility of pretherapy interventions and the management of acute and chronic oral complications. They also identified several critical areas to be addressed in future studies. The full Consensus Statement appears in this volume as well.

Clinical Investigations and Patient Care Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892.

Consensus Statement: Oral Complications of Cancer Therapies

National Institutes of Health Consensus Development Panel

More than 1 million Americans will develop cancer during 1989. These newly diagnosed malignancies will include 228,000 gastrointestinal cancers, 155,000 lung cancers, 143,000 invasive breast carcinomas, 40,000 lymphomas, and 27,000 cases of leukemia. Also included are the estimated 30,000 cases of oral and oropharyngeal cancer.

Management of many malignancies requires local or radical surgical excision. Other forms of cancer treatment may be employed, e.g., radiation therapy, chemotherapy, and bone marrow transplantation (BMT). Unfortunately, most cancer treatments affect normal as well as neoplastic cells and tissues. As treatments have become intensive and therapeutically successful, the effects on normal tissues have increased. The oral cavity is a very frequent site of such side effects. As a result of treatment, as many as 400,000 patients may develop oral complications that may be acute or chronic in nature. The more powerful the treatment modalities, the greater the risk of morbidity.

At a minimum, oral complications are painful, diminish the quality of life, and may lead to significant compliance problems, often discouraging the patient from continuing treatment. Cancer treatments may produce a breach in mucosal integrity, allowing pathogenic organisms to spread systemically, further compromising the patient's health. At times, levels of oral morbidity may interfere with oncologic therapy, necessitating suspension of therapy until such complications resolve.

Side effects of radiation therapy to the head and neck may be noted as early as the first week. The potentially devastating occurrence of osteoradionecrosis in the irradiated patient has yet to be widely addressed in terms of multicenter, collaborative studies. The prevention and management of this and other oral complications remain incompletely resolved clinical issues.

BMT is an evolving cancer management tool with frequent oral complications. Although BMT was once considered a desperate measure and reserved for treatment of end-stage leukemia, it is now used routinely as an effective tool for treatment of several other cancers. There is the possibility of secondary dysfunctions of the oral cavity both before and after actual transplantation. The stomatotoxicity of chemotherapy and total-body irradiation, the associated risk of early septicemia from oral organisms, and the possibility of acute and chronic graft-versus-host disease all may affect the ultimate treatment outcome. Literature on the subject is sparse, and there are few well-documented studies demonstrating the efficacy of treatment for the oral complications of BMT.

Pretreatment therapy for oral complications can positively affect the outcomes of cancer treatment. All members of the cancer treatment team should be fully informed of the oncologic treatment plan. Oral care should be initiated at the outset of cancer treatment with the goal of reducing morbidity and in many instances improving compliance.

The above clinical considerations prompted the formulation of several questions that served as the structural framework for this 2-day conference. The sponsors of this conference were the National Institute of Dental Research, the National Cancer Institute, the Office of Medical Applications of Research, the Clinical Center of the National Institutes of Health, and the Food and Drug Administration. Speakers, panelists, and members of the audience delivered and discussed new data, clinical experiences, and existing information that was used to formulate the statement in response to the following questions:

- What are the oral complications of cancer therapies?
- Is there a role for pretherapy interventions affecting the oral cavity in reducing the incidence of oral complications in the cancer patient?
- Which pretreatment strategies are optimal to prevent or minimize oral complications?
- What are the most effective strategies for management of acute oral complications occurring during cancer therapy?
- What are the indicated strategies for management of chronic oral complications following cancer therapy?
- What are the directions for future research?

Absent from the discussion and consensus document are the broad and important areas of postsurgical management, including surgical reconstruction and maxillofacial prosthodontic treatment. Both the surgical and prosthodontic considerations were thought to be significant but beyond the scope of this conference.

QUESTIONS AND ANSWERS

What are the oral complications of cancer therapies?

Surgical removal of anatomical structures in the head and neck region compromises oral function to varying degrees. In chemotherapy, most complications are the result of myelosuppression, immunosuppression, and direct cytotoxic effects on oral tissues. Major clinical problems in the oral cavity that are associated with chemotherapy include mucositis, local or systemic infection, and hemorrhage. Total body irradiation and radiation for head and neck cancer have both direct and indirect effects on oral and related structures. The oral complications of radiotherapy to the salivary glands, oral mucosa, oral musculature, and/or alveolar bone include growth and developmental abnormalities, xerostomia, rampant dental caries, mucositis, taste loss, osteoradionecrosis, infection, dermatitis, and trismus. It is the recognition of the risk of these complications and their relation to outcome that prompts the discussion and necessitates agreement on the best means of management.

These complications result from the aggressive treatment of cancer; many would not occur if cancers could be detected and treated at an early phase. The emphasis of this conference on the prevention and treatment of complications should not detract from the basic goal of prevention and early detection of cancer.

Is there a role for pretherapy interventions affecting the oral cavity in reducing the incidence of oral complications in the cancer patient?

Oral complications resulting from anticancer therapies can significantly affect morbidity, the patient's tolerance of treatment, and the quality of life. Death can sometimes result from severe oral complications. There is a role for pretherapy intervention in reducing the incidence and severity of oral complications. Data presented at the conference convincingly demonstrated that appropriate interventions can significantly lessen morbidity and possibly decrease mortality.

There is evidence that preexisting oral disease unrelated to cancer or therapy may increase the risk of oral complications. Before the initiation of cancer therapy, a comprehensive pretreatment dental evaluation is mandated. The following objectives should be fulfilled:

- Establish baseline data with which all subsequent examinations can be compared.
- Identify risk factors for the development of oral complications.
- Develop strategies to avoid treatment complications during and following cancer therapy.
- Perform necessary dental treatment to reduce the likelihood of oral complications induced by cancer treatment.

Which pretreatment strategies are optimal to prevent or minimize oral complications?

Many pretreatment strategies are available to minimize or prevent oral complications. These afford the clinician a unique opportunity to ameliorate the side effects induced by cancer therapy. Pretreatment strategies include evaluation, treatment of preexisting dental disease, patient and family education and counseling, prevention of oral mucosal infections, interventions to modify salivary gland dysfunction, reduction of iatrogenic and disease-related neutropenia, and prevention of mucositis.

A comprehensive patient examination is required to identify preexisting oral problems that have the potential to affect the course of cancer therapy. To satisfy the objectives of the examination, the following data must be obtained for patients at risk of oral complications: cancer diagnosis, medical history, dental history, dental charting, periodontal charting, appropriate radiographs, and nutritional status. Some clinicians may wish to include volumetric assessment of resting and stimulated whole saliva. Additionally, study models could be obtained when deemed appropriate.

Potentially complicating oral disease should be identified and corrected as early as possible before commencement of anticancer therapy. Significant problems include poor oral hygiene, third-molar pathology, periapical pathology, periodontal disease, dental caries, defective restorations, ill-fitting prostheses, orthodontic appliances, and any other potential sources of irritation.

Sources of infection and irritation are important targets for early intervention. At the initial dental evaluation, all cancer patients should undergo thorough oral hygiene procedures, including root planing, scaling, and curettage. These procedures are beneficial in reducing the incidence of oral complications by removing bacteria that can result in local and systemic infection. The neutrophil and platelet counts must be considered before any patient undergoes an invasive procedure. This intervention should be supplemented by daily plaque removal, including toothbrushing with a fluoride toothpaste and flossing, if this can be tolerated by the patient. Additionally, the use of topically applied fluorides and chlorhexidine mouth rinse has shown clinical benefit in the prevention and control of dental caries and plaque.

Dental foci may be potential sources of systemic infection and should be eliminated or ameliorated. Treatment may include dental extractions or endodontic therapy. Ideally, dental procedures, but especially dental extractions, should be completed at least 14 days before cancer therapy begins if the patient's condition permits.

Most of the pretreatment as well as treatment protocols aimed at preventing or ameliorating the oral complications of anticancer therapy require patient adherence to prescribed oral hygiene procedures. Patient and family education, counseling, and motivation are critical to the success of any preventive pretreatment strategy. The patient must be cognizant of the potential side effects of the anticancer regimen. The rationale for pretreatment strategies must be explained to encourage patient adherence to the therapy.

Bacterial and fungal surveillance cultures are not necessary for routine patient management. Cultures should be made of suspicious lesions. The use of prophylactic acyclovir should be considered for seropositive patients at high risk for reactivation of herpes simplex virus infection, i.e., BMT patients and possibly other patients with prolonged, profound myelosuppression. The prophylactic use of acyclovir in patients who are at lower risk is probably not indicated and carries a low risk of development of acyclovir-resistant strains. Although acyclovir is a relatively safe drug, it may have side effects, including renal dysfunction and, rarely, central nervous system toxicity.

Salivary gland dysfunction is one of the most common sequelae of head and neck cancer treatment. At present, there are no agreed upon pretreatment strategies to prevent or minimize xerostomia. However, studies are being conducted to evaluate various techniques, including radioprotective agents and drugs such as pilocarpine that can maintain or enhance salivary gland function during radiation. The latter approach appears to be the most promising for future clinical applications.

Pretreatment strategies to reduce iatrogenic and disease-related neutropenia in cancer patients are under investigation. A pilot trial of recombinant human granulocyte colony-stimulating factor[1] administered to patients during chemotherapy resulted in restoration of the neutrophil count and function and a decrease in severity of mucositis. Mucositis is a universal and often painful consequence of chemotherapy and radiotherapy to the head and neck. At present, there is no other agent that is effective in preventing therapy-related mucositis. Randomized clinical trials addressing this problem are in progress.

[1]The paper on this topic is not included in this volume.

What are the most effective strategies for management of acute oral complications occurring during cancer therapy?

Acute oral complications occurring during treatment are related to the type of cancer and form of therapy. These problems have several different clinical presentations, including mucosal inflammation and ulceration of varying etiologies, oral candidiasis, viral and bacterial infections, dental or periodontal infections, and mucosal bleeding. Treatment of oral infections is important to reduce the debilitating symptoms associated with these lesions and to minimize the risk of systemic bacterial or fungal infections.

Mucosal inflammation and ulceration

Radiation therapy for head and neck cancer causes mucositis, which can progress from erythema to ulceration. Chemotherapy given in conjunction with radiation may accelerate the onset and increase the severity of radiation mucositis. No currently available drugs can prevent mucositis. Radiation-induced mucosal changes can be distinguished from other similar-appearing lesions by their occurrence within the radiation field. Appropriate cultures and smears may be necessary to diagnose fungal infection in the presence of radiation mucositis. Several alternative drugs are available for antifungal therapy; however, prolonged dental contact with nystatin solution, nystatin pastilles, or clotrimazole oral troches may lead to dental caries because they contain large quantities of sugar.

Chemotherapy that does not result in profound myelosuppression can nevertheless cause mucosal ulceration by directly damaging the epithelium. The most commonly associated agents are antimetabolites such as methotrexate, 5-fluorouracil, and purine antagonists. Antitumor antibiotics, hydroxyurea, and procarbazine can also cause nonspecific mucosal ulceration.

Oral ulceration may be associated with the underlying cancer, particularly in acute leukemias, and with severe neutropenia from any cause. In these cases, the diagnosis is dependent on recognizing the association and ruling out infection. In a high percentage of patients undergoing BMT, oral mucosal lesions may occur as part of acute or chronic graft-versus-host disease. These lesions may take several forms, including erythema, lichenoid change, ulceration, and hyperkeratosis. Therapy depends on management of the underlying disease.

There are also many untested topical oral preparations that claim to reduce the symptoms of oral mucositis. The efficacy and safety of these agents have not been established. Ingredients in these combinations have included diphenhydramine hydrochloride, kaolin and pectin, magnesium sulfate, antacids, sucralfate, corticosteroids, dyclonine, and lidocaine hydrochloride. In patients who have trouble eating because of severe oral mucositis, local and/or systemic pain control may be necessary.

Viral infection

Herpes simplex virus (HSV) is the most common viral pathogen associated with oral lesions in patients receiving myelosuppressive chemotherapy or BMT. A large number of patients have had prior infection with HSV, as evidenced by the presence of HSV antibodies in the serum of 30%–100% of adults in the general population. Under conditions of immunosuppression, the latent virus is often reactivated, leading to severe oral and occasionally disseminated infections. Approximately 50%–90% of BMT patients who are seropositive for HSV will develop HSV infections, usually within the first 5 weeks after transplantation. Similarly, a large proportion of patients with acute leukemia or others receiving intensive chemotherapy will experience reactivation of HSV during periods of immunosuppression.

In contrast to HSV infections in immunocompetent individuals, HSV infections in the immunocompromised host are associated with severe ulcerations that may occur on any oral mucosal surface. In immunocompromised patients, the mucositis associated with HSV is more painful, severe, and prolonged than mucositis uncomplicated by viral infection. HSV ulcerations may be the portal of entry for bacterial and fungal pathogens. In addition, the virus may cause esophagitis and, rarely, disseminated infection.

HSV infections are often difficult to diagnose on clinical grounds alone because it may be difficult to differentiate them from mucosal lesions of other etiologies. Due to the morbidity associated with HSV infections and because effective antiviral therapy is available, it is advisable to perform viral cultures for immunosuppressed patients. Cytologic and newer diagnostic tests for the presence of viral antigens may be useful for rapid diagnosis of HSV infections. For patients whose presumptive diagnosis is oral HSV infection, it is reasonable to initiate therapy with either oral or intravenous acyclovir while awaiting the results of viral diagnostic tests. The intravenous route may be preferred for severe infections and for patients unable to take oral medications.

Oral candidiasis

Several types of oral mucosal lesions are caused by overgrowth and infection by *Candida* species, including pseudomembranous candidiasis (removable white plaques), chronic hyperplastic candidiasis (leukoplakia-like white plaques that do not rub off), chronic erythematous candidiasis (patchy or diffuse mucosal erythema), and angular cheilitis. Fungal cultures, potassium hydroxide smears, and gram-stained smears are helpful diagnostic tools. The white, raised, removable plaques of the pseudomembranous form of candidiasis are most obvious to the examiner. Diagnosis can be confirmed by a potassium hydroxide smear. These organisms may infect other sites in the gastrointestinal tract and cause esophagitis or diarrhea. In neutropenic patients, mucosal infection with *Candida* spp. may lead to systemic infection.

Topical forms of therapy for oral candidiasis include nystatin and clotrimazole. Pseudomembranous candidiasis can usually be treated with topical nystatin. Lesions of chronic oral candidiasis usually require much longer treatment, especially in patients with severe chronic xerostomia resulting from head and neck radiation therapy. In more extensive infections, such as esophagitis, oral ketoconazole may be effective. For infections not responding to the above measures, a course of low-dose intravenous amphotericin B may be indicated. Disseminated candidiasis should be managed with intravenous amphotericin B.

Baterial infections

Bacterial organisms in the mouth can cause localized infections, including acute sialadenitis of major salivary glands, periodontal abscess, pericoronitis, or other mucosal or dental

infection. These problems usually require empiric treatment with selected antibiotics, but gingival and periodontal lesions usually require additional treatment by local debridement of bacterial plaques.

Systemic infection is a major cause of morbidity and mortality in neutropenic patients. In some cases, the oral cavity may be the portal of entry for bacterial pathogens. Whether a source of infection can be identified or not, empiric, broad-spectrum antibiotic therapy must be initiated promptly in the febrile neutropenic patient. There are several different antibiotics or antibiotic combinations that may be appropriate in this setting. Because *Pseudomonas* infections are associated with a high mortality rate in patients with neutropenia, the empiric regimen should include antibiotics that adequately treat this organism.

Mucosal bleeding

Mucositis due to any cause may be accompanied by oral bleeding, especially during severe thrombocytopenia caused by leukemia, lymphoma, or myelosuppression. Disseminated intravascular coagulation is another important potential cause of thrombocytopenia or hemorrhage in immunocompromised patients. Severe thrombocytopenia may predispose patients to bleeding from routine mechanical oral hygiene procedures. In addition, these procedures may increase the risk of septicemia in patients with severe neutropenia. In these patients, dental plaque can be effectively managed by daily mouth rinsing with a chlorhexidine solution.

What are the indicated strategies for management of chronic oral complications following cancer therapy?

The therapeutic modalities used in the treatment of malignancy can result in changes in healthy tissues arising long after treatment has been completed. These sequelae must be addressed for the remainder of the patient's life.

Xerostomia is an example of such a problem in patients receiving therapy for head and neck or other forms of cancer. Total-body irradiation, especially local irradiation to oral structures, may irreversibly affect the production of saliva by both the major and minor salivary glands. The magnitude of this problem depends on the radiation dose and volume of tissue exposed. Significant xerostomia is not encountered as frequently in patients treated with chemotherapy. Concomitantly administered medications such as psychotropic and antiemetic medications should be evaluated for their xerogenic potential.

Chronic graft-versus-host disease is associated with xerostomia. Painful lichenoid lesions can also develop in these patients and compromise therapy unless controlled by immunosuppressive therapy. Long-term cyclosporine can lead to gingival hypertrophy.

There are no widely used diagnostic criteria to estimate the degree or extent of xerostomia. We are still primarily dependent on subjective impressions by both patient and clinician. A dry mouth may affect speech, taste, nutrition, and the patient's ability to tolerate dentures or other oral prostheses. Saliva also contains antimicrobial compounds and is important in the mechanical removal of pathogens from the mouth. As a consequence of decreased saliva production, there may be overgrowth of caries-producing organisms. This may have devastating effects on the dentition, even in individuals without a history of dental caries. In addition, an increase in the frequency of candidiasis and in the severity of gingival or periodontal infections has been observed in some patients.

Management of chronic xerostomia involves a combination of strategies:

- Continuous maintenance of effective oral hygiene to reduce colonization and proliferation of oral pathogens.
- Use of water or saliva substitutes to keep the mouth moist.
- Stimulation of residual salivary parenchyma to produce more saliva.

Intensive oral hygiene methods and the use of an adequately protective topical fluoride are the most important methods for preventing the dental complications of xerostomia.

Several saliva substitutes are being tested. Ideally, these should reduce patient discomfort, be long-lasting, and substitute for salivary components that are necessary for the maintenance of mucosal and hard tissue integrity. There is a need for more effective preparations and more data on the long-term benefits of this form of therapy.

Sialogogues, such as pilocarpine and anetholetrithione, alone or in combination, are being tested to stimulate the formation of saliva. The data suggest that this approach benefits patients who have some residual functional salivary tissue, resulting in a steady increase in salivary flow and symptomatic improvement. These drugs appear to be well tolerated; side effects are minimal and readily controlled. The effectiveness of sialogogues in reducing the long-term ravages of xerostomia (e.g., radiation caries) has not been documented.

The long-term effects of radiation therapy to the head and neck region include obliterative endarteritis with resultant tissue ischemia and soft tissue fibrosis. These changes may progress with time and never resolve. Surgical wounds in the irradiated area heal poorly, and chronic radiation ulcers may develop. Fibrosis of the muscles of mastication and the temporomandibular joint, while uncommon, may result in trismus. However, recurrent tumor must be ruled out.

Osteoradionecrosis (ORN), a relatively uncommon clinical event, is a consequence of hypovascularity, the cytotoxic effects of radiation on bone-forming cells and tissue, and is associated with hypoxia of the affected bone. As a consequence, when bone is injured, it is unable to heal and becomes susceptible to secondary infection. This process can progress to pathologic fracture, infection of the surrounding soft tissues, and oral-cutaneous fistula formation. It is characterized by severe, constant pain. The risk of developing ORN continues lifelong. Chemotherapy does not increase the risk of ORN.

The initiating injury resulting in ORN is frequently the extraction of a tooth from an irradiated mandible. For this reason, all teeth that might have to be removed should be extracted before radiation therapy begins. If clinical conditions permit, at least 2 weeks, and ideally 3 weeks, should be allowed for adequate healing between the extraction and the commencement of radiation therapy. Healthy teeth should be preserved. Dentures causing ulceration of the atrophic mucosa over the mandible can initiate ORN. Spontaneous ORN can also occur without any obvious injury to the irradiated mandible.

Traditional treatment of ORN with antibiotics and surgical debridement frequently fails, with progressive involvement of the remaining mandible. The keystone of the treatment of ORN is the provision of adequate tissue oxygenation in the damaged bone. This is best done by using hyperbaric oxygen therapy (HBO). Multiple treatments are required. Early stages of ORN

without fractures or fistulae may be cured by HBO alone. More advanced cases require, in addition to HBO, sequestrectomy or partial mandibulectomy with eventual bone grafting.

In the event that dental extraction is required following radiation, meticulous surgical technique and antibiotic prophylaxis are necessary. For patients who are thought to be at particularly high risk of developing ORN, preextraction HBO should be considered. An alternative to postirradiation extraction is endodontic therapy.

Complications in the pediatric population

Oral complications arising from the treatment of cancer in children have characteristics in common with those observed in adults. However, because children are actively growing and developing, cancer treatment creates additional long-term problems unique to the pediatric patient. As modern therapy results in increasingly improved survival for a variety of pediatric cancers, long-term sequelae of treatment are beginning to emerge. Some reports indicate that the frequency of oral complications in pediatric patients may be higher than in adults. The nature and severity of these treatment sequelae depend on a number of factors: the type and location of the tumor, the age of the patient, the dose of radiotherapy, the aggressiveness of chemotherapy, the status of oral and dental health, and the level of dental care before, during, and after therapy.

Chronic problems involving target tissues are impaired growth and development of hard and soft tissues, which may result in orofacial asymmetry, xerostomia, dental caries, trismus, and a wide variety of dental abnormalities. The latter include delayed tooth eruption, altered dental root development with shortening and thinning of the roots, enamel opacities, enamel grooves and pits, small teeth, small crowns, and failure of tooth development and eruption. In teeth with underdeveloped roots secondary to cancer therapy, even minimal periodontal disease will result in early loss of teeth. In general, the principles applicable to the preventive and active treatment of xerostomia, dental caries, and trismus in adults appear to be applicable to children as well. However, evaluation of the efficacy and long-term consequences of these various strategies has not yet been carried out on a large scale.

These children may have lifelong dental problems requiring periodontic, orthodontic, prosthodontic, or orthognathic procedures. Supervised, consistent oral care, meticulous hygiene, and a regular dental recall schedule (to uncover problems early and determine the need for dental intervention) are key to maintenance of dental health care in children cured of their cancer. In addition, the emotional and psychological consequences of orofacial deformities and oral dysfunction in these children deserve more attention as increasing numbers of these patients survive.

The potential for development of secondary malignancies in these survivors is a serious delayed sequela of successful cancer therapy. Although a majority of secondary malignancies reported in children consist of leukemia or lymphomas, soft tissue and bone sarcomas can occur in irradiated sites. The possibility of secondary malignancies arising in these children should heighten the clinician's awareness of this problem.

Providing education and information to the patient and family is essential for maximum treatment compliance. Direct involvement of the family is thought to result in improved adherence to treatment protocols, thereby enhancing the patient's quality of life.

The therapeutic team should be multidisciplinary and sensitive to the patient's emotional and physical needs related to the illness. Patients traumatized by the loss of normal oral function, the presence of pain, nausea, and impairment of eating, and a life-threatening illness can become depressed. The therapeutic team should provide information to increase the patient's and family's understanding of the medical/oral condition, the treatment plan, and the consequences of treatment as a preventive measure. Methods of educating the patient and family should be individualized to the diagnosis and specific needs. Patience and positive reinforcement are important.

What are the directions for future research?

- Devise accurate, quantifiable, and reproducible criteria for assessing and classifying oral complications of cancer therapy.
- Determine incidence and prevalence of oral complications related to different types of anticancer therapies and related risk factors.
- Study the mechanisms of cancer treatment injury to the hard and soft oral tissues at the molecular and cellular level and determine how these affect the oral environment.
- Delineate the role of latent HSV reactivation in the pathogenesis of mucositis due to radiation therapy and chemotherapy of solid tumors.
- Study the frequency, clinical significance, and mechanisms of development of acyclovir resistance by HSV.
- Develop radioprotective and chemoprotective agents.
- Define the role of biological response modifiers (e.g., recombinant human granulocyte colony-stimulating factor) in the prevention of myelosuppression and the influence of these agents on oral tissues and oral complications.
- Define and further document through prospective studies the effectiveness of initiating current pretreatment oral care protocols on the incidence, severity, and extent of oral complications of cancer management.
- Develop more effective sialogogues and saliva substitutes and evaluate their effectiveness in preventing the complications of xerostomia.
- Determine the most effective strategies to ensure patient compliance with therapeutic regimens.
- Define the role of the family support unit in the diagnosis, prevention, and treatment of oral complications of cancer treatment.
- Conduct further studies on the role of the oral cavity as a source of systemic infection.
- Conduct controlled studies to determine and test optimal antifungal therapies.
- Define patient populations that will benefit from prophylactic antiviral therapy.
- Define the role for oral antimicrobial agents in the prevention of infection in neutropenic patients and the effect of such prophylaxis on oral and gastrointestinal flora.
- Devise controlled studies of chlorhexidine and other agents for the control of mucositis in specified patient populations.
- Determine whether oral markers can serve as a predictor of problems of other organs.
- Develop more precise protocols for use of HBO.

- Study disorders of taste perception in patients undergoing cancer therapy.
- Determine the cost-effectiveness of preventive, diagnostic, and therapeutic management of oral complications.
- Study the effect of different topical fluoride preparations to determine the most effective forms and dosage schedules.

The panel believes that many research goals can be achieved through coordination of committed members of the dental, medical, and nursing professions who are already actively involved in clinical investigations. Through such cooperative efforts, patients enrolled in ongoing investigations could serve to answer these important questions.

Deep concern exists that appropriate dental care may not be available due to a significant lack of appropriate levels of third-party reimbursement. This is particularly true when dental treatment required as part of the overall cancer management plan is not reimbursed.

CONCLUSIONS AND RECOMMENDATIONS

- All cancer patients should have an oral examination before initiation of cancer therapy.
- Treatment of preexisting or concomitant oral disease is essential in minimizing oral complications in all cancer patients.
- Prophylactic acyclovir is beneficial for selected patients to prevent HSV reactivation.
- Precise diagnosis of mucosal lesions and specific treatment of fungal, viral, and bacterial infections are essential.
- Mucosal ulcerations should alert the cancer team to the risk of systemic infection.
- Currently, the best treatments for chronic xerostomia include regular use of topical fluorides, attention to oral hygiene, and sialogogues.
- ORN can be prevented. When present, it is best managed with HBO alone or with surgery.
- In the pediatric population, it is important to recognize the long-term consequences of radiation therapy, which include dental and developmental abnormalities and secondary malignancies.
- Studies of oral complications should be incorporated into ongoing and future cooperative clinical oncology group protocols.
- Disseminate information about oral complications of cancer therapies and develop strategies to ensure adherence by health care providers to appropriate preventive measures.
- Develop and implement curricula relevant to oral complications of cancer therapy in schools of medicine, dentistry, dental hygiene, and nursing.
- Direct family involvement in patient care is encouraged for maximum treatment compliance.

I. Overview

Description and Incidence of Oral Complications

Samuel Dreizen

No part of the body reflects the complications of cancer chemotherapy as visibly and as vividly as the mouth. The infectious, hemorrhagic, cytotoxic, nutritional, and neurologic signs of drug toxicity are reflected in the mouth by changes in the color, character, comfort, and continuity of the mucosa. The stomatologic complications of radiotherapy for oral cancer are physical and physiological in nature, transient or lasting in duration, and reversible or irreversible in type. Some linger as permanent mementos long after the cancer has been destroyed. They stem from radiation injury to the salivary glands, oral mucosa, oral musculature, alveolar bone, and developing teeth. They are expressed clinically by xerostomia, trismus, radiation dermatitis, nutritional stomatitis, and dentofacial malformation. In both cancer chemotherapy and cancer radiotherapy, the oral complications vary in pattern, duration, intensity, and number, with not every patient developing every complication. [NCI Monogr 9:11–15, 1990]

No anticancer therapy is completely innocuous. While each is designed to be lethal to cancer cells, normal cells are invariably killed as well. Thus, each therapy can exact a steep price from the patient that may preclude further treatment, jeopardize survival, or irrevocably alter the quality of life. The mouth of the patient with cancer is a common target for treatment-related side effects. Both anticancer chemotherapy for disseminated neoplasms or as an adjunct to the surgical or radiologic eradication of local lesions and anticancer radiotherapy for mouth malignancies create a host of stomatologic disruptions, the description and incidence of which are detailed in this article.

STOMATOTOXIC MANIFESTATIONS OF CHEMOTHERAPY

Antitumor drugs cannot distinguish between malignant cells and normal cells and are thus potentially damaging to both. The basic rationale for cancer chemotherapy is to maximize the destruction of tumor cells and to minimize the harm to normal cells. Unfortunately, many anticancer drugs have only a narrow margin of safety between the tumoricidal and toxic doses. Combining drugs with different mechanisms of action widens the scope of antitumor activity and diminishes the risk of toxicity by lowering the effective dose of each component. Combination chemotherapy includes cell cycle-dependent drugs and cell cycle-independent drugs, covering both the proliferative and vegetative phases of the cell cycle.

A rate of cell division comparable to that of fast-growing tumors and a trauma-intense environment combine to make the mouth extremely sensitive to the toxic action of antineoplastic drugs. Some act directly by metabolic interference with growth, maturation, and replacement of oral mucosal cells; others act indirectly by causing myelosuppression and immunosuppression. The direct effects are expressed clinically by mucositis involving denudation and ulceration of the mucosa; the indirect effects are expressed by oral infections and oral hemorrhages.

Although oral reactions to stomatotoxic antineoplastic drugs are generally related to dose and duration of treatment, cancer patients differ markedly in their capacity to tolerate a given amount of drug or combination of drugs. There is considerably more interpatient than intrapatient variation in this respect. Patients who develop oral toxicity during the first course of treatment will almost assuredly show identical side effects during each subsequent course unless the drugs are changed or the doses are lowered. The incidence of oral complications in paients treated for adult leukemia approaches 50% (*1*); that for patients with solid tumors ranges from 12% for carcinomas and sarcomas to 33% for lymphomas (*2*). Among adults, the predisposition to develop oral complications does not seem to be related to age, sex, or habitus. There is as yet no way to predict which new patient will develop oral problems and which will not, following the same cancer chemotherapy.

Infections

Chemotherapy-induced suppression of the stem cells that evolve into granulocytes and lymphocytes deprives patients of a substantial part of the protection provided by the immune system and makes them extremely vulnerable to bacterial, fungal, viral, and mixed infections. The greater the degree and duration of the neutropenia or lymphocytopenia, the greater the risk of infection. Patients with granulocyte or lymphocyte counts of less than 100/mm^3 have a greater than 50% chance of developing an infection in some part of the body. If this level of granulocytopenia persists for 3 weeks or more, the risk increases to 100% (*3*).

The incidence of chemotherapy-associated oral infections in adults hospitalized in the University of Texas M.D. Anderson Hospital ranges from 8.4% through 11.7%, 18.3%, and 34.2% among those treated for carcinoma, sarcoma, lymphoma, and leukemia, respectively (*4,5*). The difference between patients treated for leukemia and those treated for solid tumors in developing oral infections is ascribed to differences in the aggressiveness of the treatment, that for leukemia being much more myelosuppressive than that for solid tumors. Almost 70% of the infections in patients with solid tumors and 50% of those in patients with acute leukemia are caused by fungi, with *Candida albicans* being the precipitating organism in 96%–97% of the cases. The most common sites of oral candidiasis in chemotherapy patients are the sides and dorsum of the tongue, the buccal, gingival, and palatal mucosa, and the commissures

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of the lips. *Candida* infection is manifested by painless, pearly white, raised, curdlike strands, beads, flecks, or patches that adhere firmly to the underlying mucosa. There is a tendency for the growth to coalesce and to blanket large areas of the lining of the mouth. Forcible removal of the growth exposes a painful, raw-red, superficially ulcerated, and bleeding mucosal surface. Each fungal infection was confirmed by culturing and determining the species on selective media.

At M.D. Anderson Hospital, 25% of the oral infections in patients treated for leukemia and 10% of those in patients treated for solid tumors are caused by herpes simplex virus. Most are located on the lips, commissures, and circumoral skin. Intraorally, the most common locations are the dorsum of the tongue and palatal mucosa. The oral lesions are often heralded systemically by fever and malaise and locally by a prodrome of tingling, itching, burning, and pain that lasts for several hours before small vesicles emerge. The vesicles rupture within 12 hours, producing ulcers that may merge and eventually crust over. Often the lesions follow a chronic course, enlarging peripherally and causing extensive necrosis of the lips and mouth before undergoing a period of protracted healing (*6*). Diagnosis of herpetic infection was made on the basis of clinical appearance, positive viral cultures, or the presence of intranuclear inclusions in the epithelial cells of stained smears from suspect lesions.

Most of the oral bacterial infections that develop during treatment with antineoplastic drugs at M.D. Anderson Hospital are caused by aerobic gram-negative bacilli, specifically *Pseudomonas, Klebsiella, Serratia, Enterobacter, Proteus,* and *Escherichia* spp. Presently, they account for 15% of oral infections in patients with leukemia and 10% of those in patients with solid tumors. Lesions produced by *Pseudomonas* spp. are necrotizing and encircled by a red halo. Initially they have a dry, raised, whitish yellow center that becomes purple to black on turning necrotic. With appropriate treatment, the necrosed core sloughs off, disclosing a bright red, shiny bed of granulation tissue. The oral mucosal infections caused by the other gram-negative bacteria are clinically indistinguishable. They are identical in color, character, course, and distribution. Typical lesions are raised, creamy to yellow-white, moist, glistening, and nonpurulent, with a smooth edged growth seated on painful, red, superficial mucosal ulcers and erosions. Any part of the oral cavity may be affected, but the dorsum and undersurface of the tongue, palatal and gingival mucosa, and lips are the most common sites.

Oral staphylococcal and streptococcal infections, while not nearly as numerous at M.D. Anderson Hospital as before the introduction of the semisynthetic penicillinase-resistant penicillins, still constitute 10% of all oral infections in patients receiving cancer chemotherapy. Because of drug-induced neutropenia, lesions produced by many of these normally pyogenic bacteria present as dry, raised, verrucous, yellow-brown plaques with little or no pus. Diagnosis of bacterial infections was made by culturing samples of the lesions on selective media and determining the species by conventional methods.

Existing oral infections, such as those that accompany periodontal and pulpal disease, are often exacerbated during cancer chemotherapy. One report set the incidence of such infections in leukemic patients prior to treatment at 22% in those who practiced limited oral hygiene and at 5% in those who practiced good oral hygiene (*7*).

Mucositis

Stomatitis presenting as a mucositis of the lips, tongue, and oral mucosa occurs in almost 20% of patients treated for adult leukemia at M.D. Anderson Hospital (*8*). There is a considerably lower incidence of oral mucositis in patients given chemotherapy for solid tumors because solid tumors can be suppressed by doses substantially lower than those required for myelosuppression. All antitumor drugs that are toxic to the oral mucosa interfere with either DNA, RNA, or protein synthesis, resulting in reduced production, impaired differentiation, and accelerated detachment of the epithelial cells. The folic acid antagonists, purine and pyrimidine antimetabolites, anticancer antibiotics, hydroxyurea, and procarbazine are most culpable in this respect.

The clinical signs of chemotherapy-induced mucositis are diminished mucosal thickness and keratinization, superficial sloughing, intense redness of the involved areas, and traumatic and atraumatic ulcerations. Pain is often intense and unremitting, creating problems in food intake. The manifestations begin a few days after therapy is started, peak a week after course completion, and slowly recede unless complicated by infection, hemorrhage, or repeated drug administration.

The reactions of the oral mucosa to anticancer drugs may be local or generalized in distribution and acute to subacute in course. They are highly individualistic in pattern and rarely take an identical form in any two patients. They are indistinguishable as to specific cause, and their appearance may be altered by superimposed trauma, infection, and hemorrhage. The damage is usually reversible and self-healing after treatment is stopped.

Hemorrhages

Oral hemorrhages rank third in the constellation of oral complications of cancer chemotherapy in adults with acute leukemia treated at M.D. Anderson Hospital, with a frequency rate of 15% (*9*). The most important single contributing factor is the thrombocytopenia that results from the drug-induced myelosuppression. The lower the platelet count, the greater the possibility of oral bleeding. While oral bleeding is rare at platelet counts above 50,000/mm^3, the chances of such hemorrhages at levels below 30,000/mm^3 exceed 50%.

Thrombocytopenia is the identifiable cause in 88% of patients receiving chemotherapy who manifest bleeding of the mouth during hospitalization; disseminated intravascular coagulation is implicated in 6%, and combinations of thrombocytopenia and hypofibrinogenemia and of thrombocytopenia and vitamin K deficiency are responsible in 5.5% and 0.6%, respectively. Approximately 50% of the patients who experience oral hemorrhage after chemotherapy have coagulation factor deficiencies in the blood.

Oral hemorrhages can originate in any part of the mouth, with the lips, tongue, and gingiva the most common sites. The hemorrhages are invariably triggered by trauma sufficient to injure the capillary beds. Hemorrhages are usually dark red, oozing, and intermittent, with few or multiple bleeding points. Soft, friable clots form, break away, and reform in sequence. The bleeding that accompanies disseminated intravascular coagulation or decreases in the blood clotting factors caused by the release of thromboplastin substances into the blood following drug-provoked destruction of large numbers of white cells or drug-induced inhibition of fibrinogen synthesis clinically mim-

ics the bleeding that accompanies thrombocytopenia. Oral hemorrhages are best managed by transfusions of HLA-compatible fresh frozen platelets, cryoprecipitate, or topical coagulants until bone marrow recovery restores hemostatic control.

STOMATOTOXIC MANIFESTATIONS OF RADIOTHERAPY

The oral complications of cancer radiotherapy emanate from radiation injury to the salivary glands, oral mucosa, oral musculature, alveolar bone, and developing teeth. They are expressed clinically by xerostomia, rampant dental caries, mucositis, taste loss, osteoradionecrosis, oral infections, trismus, radiation dermatitis, nutritional stomatitis, and dentofacial malformations. The complications vary in pattern, duration, intensity, and number. Not every patient develops every complication.

Xerostomia

There is a dramatic decline in saliva production when all of the major salivary glands are included in the radiation fields. The decline is related to the dose and duration of therapy and reflects radiation-provoked inflammatory and degenerative changes in the acinar cells. The glandular architecture is replaced by ductal remnants and loose fibrous connective tissue moderately infiltrated with lymphocytes and plasma cells.

Radiation xerostomia is rapid in onset, with a greater than 50% decrease after 1 week of radiotherapy [220 rads (2 Gy)] and a greater than 75% decline after 6 weeks of treatment [6,000 rads (60 Gy)]. The xerostomia is progressive, persistent, and irreversible, reaching a greater than 95% reduction in saliva output 3 years after irradiation (*10*). When the upper limit of the radiation fields falls below the submental region, the change in salivary flow rate over the long term is minimal; when the upper limit is at the chin to mastoid line, the flow rate is markedly but not maximally reduced (*11*). When parts of the major glands are not exposed to irradiation, there is a compensatory hyperplasia of the undamaged portion in an attempt to functionally replace the destroyed cells.

Dental Caries

Dentulous patients with radiation xerostomia invariably develop ravaging dental caries unless stringent measures are taken to protect the teeth (*12*). Xerostomia deprives the teeth of an essential natural defense against dental decay. The diminution in saliva production is accompanied by the emergence of a highly cariogenic oral microflora, a sharp decrease in daily output of salivary electrolytes and immunoproteins, and a change in food consumption patterns. The microbial, chemical, immunologic, and dietary changes add up to an enormous increase in caries that is seemingly independent of past caries history.

Mucositis

The oral mucosa responds to irradiation by a series of changes that are related to dose and duration of therapy. The onset, intensity, and chronology of the oral mucosal reactions vary with the individual and depend on the fractionation and protraction of the dose, angulation of the beam, location of the lesion, and degree of oral hygiene. Radiation mucositis usually first appears at the beginning of the second week of treatment, intensifies thereafter, and may persist for 2 to 3 weeks after completion of radiotherapy.

Initially the mucosa in the path of radiation appears reddened and swollen, due to irritative hyperemia and edema. As treatment continues, the mucosa becomes denuded, ulcerated, and covered with a fibrinous exudate. Pain, burning, and discomfort are commonly present at rest and are greatly intensified by contact with coarse or highly seasoned foods. Involvement of the pharyngeal musoca produces difficulties in swallowing and speaking.

Taste Loss

Patients undergoing radiotherapy for oral cancer quickly lose their sense of taste. The rate of loss is smoothly exponential up to an accumulated dose of 3,000 rads (30 Gy) and then slows as acuity for all four tastes (sweet, sour, bitter, and salty) approaches zero (*13*). Patients exposed to more than 3,000 rads can barely identify a sucrose solution equivalent to 25 teaspoons of sugar per cup as sweet, a solution half as concentrated as household vinegar as acid, a solution 1,500 times stronger than carbonated quinine water as bitter, and a highly concentrated sodium chloride solution as salty. Damage to the microvilli and outer surface of the taste cells has been proposed as the operative mechanism for taste loss. In most instances, taste acuity is partially restored 20 to 60 days after radiotherapy and is fully restored within 2 to 4 months postirradiation. Some patients, however, are left with a residual hypogeusia.

Osteoradionecrosis

The incidence of osteoradionecrosis of the mandible or maxilla in patients given radiotherapy for head and neck malignancies at M.D. Anderson Hospital has ranged from 14% to 22% (*14*). Histologically, osteoradionecrosis is manifested by destruction of osteocytes, absence of osteoblasts from the margins of bone spicules, and lack of new osteoid. The regional blood vessels are thickened by fibrosis, endarteritis, and periarteritis. The bone marrow is infiltrated with lymphocytes, plasma cells, and macrophages. There is no definite line of demarcation between the dead and living bone. The devitalized bone is subject to infection and sequestration. Clinically, the necrotic bone is denuded, greenish gray, suppurative, foul smelling, and extremely painful at rest, at night, and during chewing.

Patients are most vulnerable to osteoradionecrosis of the jaws in the first 2 years after radiotherapy, although the complication can occur at any time thereafter. Because of the difference in richness of blood supply, the mandible is much more prone to osteoradionecrosis than is the maxilla. Osteoradionecrosis is most apt to occur in patients who feature the bone necrosis profile formulated by Daly and Drane (*15*), notably inadequate healing from preradiotherapy surgery, irradiation of oral malignancies in proximity to bone, high-dose irradiation, use of both external radiation and intraoral implants, poor oral hygiene and continued use of mouth irritants, poor patient compliance in caring for hard and soft mouth tissues, surgery in the irradiated area, use of poorly fitting prosthetic appliances, failure to prevent trauma to irradiated bone, and the presence of contributing physical and nutritional factors.

Infections

Irradiation has a detrimental effect on the oral mucosa that creates a favorable environment for the growth of *Candida albicans*, the most common oral infectant in patients given radiotherapy for cancer of the mouth (*16*). The clinical signs and symptoms of the ensuing candidiasis are the same as those described previously for patients receiving chemotherapy.

The role of infection in the pathogenesis of osteoradionecrosis of the jaws is controversial. Some consider microbial infection an integral part of the process (*17*); others claim that microorganisms play only a contaminant role (*18*). There is general agreement that osteoradionecrosis is best managed by preventing infection of exposed nonvital bone and soft tissue and promoting healing of the surrounding mucosa in an attempt to achieve coverage of the bone.

Trismus

Trismus, characterized by tonic spasms of the muscles of mastication, may develop when these muscles or the temporomandibular joint are included in the radiation fields. This disorder severely limits mouth opening and has been attributed to muscle fibrosis and to fibrotic changes in the temporomandibular joint capsule (*15*). Trismus may become evident during radiotherapy but is usually manifested 3 to 6 months after treatment. Patients should be started on prophylactic mouth-opening exercise if the masticatory muscles are to be heavily irradiated. Once trismus has developed, more intensive exercises and prosthetic aids may be needed to regain lost interarch space. If these fail, radical corrective surgical procedures may be beneficial.

Dermatitis

Radiodermatitis is not an infrequent sequela of radiotherapy to the head and neck. First-degree acute radiodermatitis is characterized clinically by erythema and edema accompanied by burning and pruritus that begins shortly after irradiation is initiated, intensifies with time, and subsides 2 to 3 weeks after cessation of treatment, leaving hyperpigmentation and temporary or permanent hair loss in the affected areas as residues. Second-degree acute radiodermatitis is more intense and associated with vesiculation, erosion, and superficial ulceration in addition to the erythema and edema. Spontaneous healing occurs over a 6-week to 3-month period. Permanent alopecia, scarring, and hyperpigmentation may remain. Third-degree acute radiodermatitis is typified by necrosis and exfoliation of the skin, with painless punched-out deep ulcers.

In chronic radiodermatitis, the involved skin appears dry, smooth, shiny, atrophic, necrotic, telangiectatic, depilated, and ulcerated.

Nutritional Stomatitis

Many of the patients who receive radiotherapy for oral cancer become nutritional casualties. Profound loss of appetite is an early and sustained reaction to radiation-provoked mucositis, xerostomia, dysgeusia, dysphagia, nausea, and vomiting. Eating becomes a painful and pleasureless task. Food selection is restricted to bland items often lacking in essential nutrients. When severe enough and prolonged enough, the inadequate intake will precipitate a nutritional-deficiency stomatitis. Patients receiving radiotherapy for oral cancer need professional nutritional counseling from the very beginning of treatment to maintain proper nutritional status (*19*).

Dentofacial Malformations

Children given radiotherapy during tooth development are at risk of dental malformations, presenting as crown and root dwarfism, root shortening, abnormal root curvature, rootless teeth, and incomplete calcification (*20*). The reactions depend on dose and stage of development. Radiotherapy may also retard the growth of the facial bones through damage to the growth centers. Clinically, the retardation is expressed as micrognathia, retrognathia, and malocclusion (*21*).

SUMMARY

The oral complications of cancer therapy are physical and physiologic in nature, transient or lasting in duration, and reversible or irreversible in type. Some linger as permanent mementos long after the cancer has been destroyed. To improve the quality of life of such patients, each treatment-related oral problem must be knowledgeably evaluated, expeditiously treated, and competently controlled.

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Oral Defenses and Compromises: An Overview

Sol Silverman, Jr.

Compromises of oral defenses as a result of cancer therapy include interruption of an intact oral mucosa, alterations of saliva, inappropriate or inadequate inflammatory responses, and diminished soft and hard tissue vascularization. The severity of compromise depends on the type and extent of treatment, involving surgery, radiation, chemotherapy, or combinations of these modalities. The resultant complications in turn depend on the aggressiveness of the planned treatment, which in turn depends on tumor stage and type. Also, unknown patient biologic factors play some role in these responses and account for patient-to-patient differences.

It must be remembered that the prime therapeutic considerations relate to tumor control. Although many malignancies require aggressive treatment for control regardless of stage, many cancers require less aggressive treatment when the diagnosis is made at an early stage. Treating lesions at earlier stages, when they generally require less aggressive treatment, would significantly reduce the complications of cancer therapy. Therefore, early detection is important to the problem of compromised oral defenses and complications (*1*).

The problem of compromised host defenses increases each year, partly owing to newer and more radical therapies to improve cancer survival and cure rates. Additionally, there are yearly increases in the number of cancer cases diagnosed in the United States, with more than 1 million new cancers estimated for 1989 (table 1). While many more tumors can be diagnosed at earlier stages by increasing both professional and public education programs, many cancers require aggressive radiation or chemotherapy; examples are leukemias and lymphomas. The current estimate for new cases diagnosed in 1989 is approximately 60,000.

Oral cancers serve as a model to describe the problems of compromised oral defenses as a result of cancer therapies. A most important aspect of oral cancer is the fact that more than half of the cases that are diagnosed each year are advanced (stages III and IV, indicating lesions larger than 4 cm, tumor invading specific adjacent structures, and/or metastatic spread). Since the cure rates overall are very poor (less than 50% of such patients survive 5 yr), treatment is usually aggressive and morbidity is marked. From recent Surveillance, Epidemiology, and End Results data, along with the new TNM staging system, advanced lesions at the time of diagnosis outnumber early lesions by more than 2 to 1 (table 2). This fact indicates the need for aggressive treatment to achieve disease control, which in turn pushes to the limit oral defense mechanisms that protect normal status.

An additional biologic factor that may play some role in cancers in general, as exemplified by oral cancer (table 3), is the fact that cancer is a disease of aging. This implies an immune surveillance system that is already somewhat compromised, which may influence tumor occurrence, staging, and host response. The large number of second primary head and neck cancers that occur in the oral cancer group also indirectly implicate susceptibility and alterations in immune regulation (table 4).

When surgery is performed for head and neck cancer, this will compromise functions due to the removal or alteration of vital head and neck structures, creating several compromises. Difficulties in diet and nutritional intake may render the host susceptible to intercurrent infections from weight loss and cachexia. Associated pain and dysphagia often contribute to this difficulty. Surgery is often used in these advanced cases in combination with radiation or chemotherapy, which magnifies the problem, particularly when the tongue and mandible are involved. Furthermore, these changes affect the patient's emotional status and often lead to despair and compromises in cooperative efforts at treatment and rehabilitation. Weight loss has been shown to be an independent prognostic indicator of survival and quality of life (*2*).

Radiation has the potential to compromise host defenses in other ways, the most prominent being the effect on salivary gland function when this tissue is included in the field of radiation (*3*). At doses that seem to vary from patient to patient, salivary gland inflammation, fatty degeneration, fibrosis, and disappearance of parenchyma complicate and alter function, usually reducing not only the amount but also the biochemistry of saliva.

The resultant xerostomia and altered saliva compromise the host by reducing protective enzymes and antibodies, resulting in acute and chronic infections (*4*) as well as further affecting dietary intake and nutrition. Radiation also damages taste buds, inducing dysgeusia and ageusia (*5*), causing patients to lose interest in food.

Radiation also alters blood supplies to oral soft and hard tissue structures by inducing vascular thromboses and fibrosis, which render the host susceptible to soft tissue necrosis and osteonecrosis (*6*). These changes often lead to severe pain and secondary infections that frequently do not respond to analgesic and antibiotic therapies. Alterations of normal epithelial mitoses, as well as the vascular compromise, cause the oral epithelium to thin, often to ulcerate, and create the basis for further pain and infection. Indirectly, this effect complicates the objective of maintaining good oral hygiene.

Chemotherapy compromises the host in many ways because it affects cells with a high metabolic rate. Therefore, the oral epithelium is selectively suppressed; spontaneous ulceration may occur, and there is poor resistance to trauma or microorganisms (*7–10*). In addition, bone marrow suppression and the induced leukopenias (usually to less than 2,000 wbc/mm^3) invite a milieu of infections and contribute further to a painful

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Table 1. Cancer in the United States: estimates for selected sites, 1989[a]

Site	No. of new cases	Male-female ratio	No. of deaths
All[b]	1,010,000	1.0	502,000
Lung	155,000	1.9	142,000
Colorectal	151,000	0.9	61,300
Lymphoma	51,800	1.1	27,400
Oral[c]	30,600	2.1	8,650
Leukemia	27,300	1.3	18,100
Larynx	12,300	4.3	3,700

[a] Data are from *CA-A Cancer Journal for Clinicians* 39:12-13, 1989.
[b] Carcinoma in situ and nonmelanoma skin cancers not included.
[c] Account for 3.1% of all new cases.

Table 2. Oral cancer: stage at diagnosis, local and national data for 1973-1984 compared[a]

SEER group	All cases		Staging (% of patients)		5-Yr survival (% of patients)	
	No. of patients	5-Yr survival (%)	Localized	Spread	Localized	Spread
Total	12,792	45	30	70	72	34
San Francisco Bay area	2,610	42	23	77	66	35

[a] Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER). Localized = stages I and II; spread = stages III and IV. Unspecified oral sites are included.

Table 3. Age and sex distribution of oral cancer cases (based on 20,115 cases)[a]

Age (yr)	% of cases	
	Male	Female
≤19	<1	<1
20-39	3	2
40-49	10	8
50-64	44	44
≥65	43	46
Total	71	29

[a] Cancers diagnosed and/or treated between 1973 and 1984 according to biostatistical information from 10 population-based tumor registries in Connecticut, Hawaii, Iowa, New Jersey, New Mexico, Utah, Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound. Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program.

Table 4. Risks for multiple oral cancers

Authors (ref No.)	No. of patients	First oral site	% of patients developing other cancers	
			Extraoral	Second oral
Fu (*13*)	153	Floor	36	15
Fu (*14*)	204	Tongue	19	19
Tepperman (*15*)	377	Floor	27	9
Silverman (*16*)	277	Oral	—[a]	18

[a] Not specified.

Table 5. Smoking and oral cancer[a]

Tobacco use	No. (%) of patients		
	At time of diagnosis	At 1 yr posttreatment	After second primary oropharyngeal cancer[b]
Yes	187 (67.5)	90 (48)	23 (25.6)
Stopped		97 (52)	13 (13.4)
No[c]	90 (32.5)	90 (100)	13 (14.4)

[a] Data obtained at the Oral Medicine Clinic, University of California, San Francisco.
[b] Mean follow-up period, 5 yr.
[c] Never smoked or stopped >1 yr before.

mucositis. Thrombocytopenia and anemias add to the problems of oral defenses and health. Oral microbial organisms have an opportunity in this environment to flourish, leading to local as well as systemic infections. Particular problems are related to activation and overgrowth of *Candida* species and herpesvirus. Additionally, the associated side effects of nausea and vomit-

ing, pain, dysphagia, and subsequent malnutrition complicate the therapy-induced host compromises.

Another host "defense" quality that is frequently compromised is behavioral in nature; patients become depressed and "unable" to comply with supportive measures to mitigate the impact of therapy (*11*). Such patients may become uncooperative in obtaining adequate nutrition, abuse alcohol and tobacco (*12*) (table 5), increase their use of narcotic and psychotropic drugs, and decrease their oral hygiene efforts.

It is evident from this discussion of the compromises induced by cancer therapies that research will play an important role in modifying these problems. Solutions will include behavioral interventions, tissue sensitizers to either increase the effectiveness of therapy or prevent therapy-induced tissue damage, and monoclonal antibodies that may accurately direct therapeutic agents to tumor cells, sparing normal tissues.

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Infectious and Noninfectious Systemic Consequences

John R. Wingard

Oral complications of cancer therapy often have systemic consequences. Pain and discomfort are common and can lower intake of fluid and nutrients, which in severe cases can lead to dehydration and malnutrition, requiring hospitalization. Oral infections are frequent accompaniments of cancer treatment. Herpes simplex virus is the most common symptomatic oral viral infection, and, in latently infected patients the virus is frequently reactivated after cytoreductive therapy. Viral (infectious) oral mucositis is often indistinguishable from noninfectious mucositis. Bacterial infections are less commonly observed today, perhaps because of the routine use of empiric broad-spectrum antibiotics; however, many episodes of septicemia in neutropenic patients apparently originate from oral microorganisms. Fungal infections are frequent and are usually due to *Candida* species. Spread to the esophagus or systemic dissemination can occur. Noninfectious oral mucositis can be used as a marker of toxic effects in other organs, especially hepatic veno-occlusive disease. In bone marrow transplant patients with mucositis, hepatic veno-occlusive disease is six times more frequent than in such patients without mucositis. [NCI Monogr 9:21–26, 1990]

Oral complications of cancer therapy occur in most patients treated for head and neck malignancies and in almost half of the patients receiving chemotherapy for non–head and neck cancers (*1–6*). Contributing factors include (*a*) direct tissue necrosis from the cytotoxic therapy, leading to local barrier breakdown; (*b*) decreased neutrophil function and immunocompetence, increasing the risk of infection; (*c*) decreased platelet function, resulting in susceptibility to hemorrhage; (*d*) physical and chemical trauma associated with eating or emesis; and (*e*) other factors, such as baseline oral pathology unrelated to the cancer (e.g., periodontal disease) and graft-versus-host disease in patients given allogeneic bone marrow transplants.

NONINFECTIOUS CONSEQUENCES

Oral complications can have a variety of systemic consequences, as shown in table 1. Pain and discomfort are common, and the severity of these symptoms appears to correlate with the dose intensity of the cytoreductive treatment. Narcotics are often needed for pain control and, in severe cases, may need to be given parenterally.

Along with nausea, patients most often report oral pain as a reason for reduced acceptability of chemotherapy. This reaction has assumed greater importance today, when chemotherapy is often used adjuvantly. In the adjuvant setting, the benefit of chemotherapy is not felt immediately and the costs (in terms of toxicity) loom greater in the patient's decision whether to accept the treatment. Thus, the patient has to compromise quality of life at a time when the threat of death from malignancy is not immediately obvious in return for a potential benefit later. Efforts to minimize the oral toxicity of treatment will have the desirable benefit of encouraging greater patient compliance with the overall treatment plan.

Oral pain of a significant degree generally results in reduced oral intake of fluids and nutrients. In severe cases, this can lead to dehydration and malnutrition. For patients given intensive chemotherapy, hospitalization to provide intravenous fluids or parenteral hyperalimentation is usually necessary. These supportive measures add to the high cost of cancer treatment and place the patient at risk of nosocomial infection and other complications associated with intravenous catheters.

INFECTIOUS CONSEQUENCES

Oral infections are frequent accompaniments of cancer treatment. Viral, bacterial, and fungal infections are all common. Table 2 lists the major oral infectious pathogens that have systemic consequences and their relative local and systemic impact.

Herpes Simplex Infections

Herpes simplex virus type 1 (HSV-1) causes the most common symptomatic oral viral infection. In many patients who are seropositive for HSV (and thus harbor latent virus), the virus is reactivated after cytoreductive therapy (*7–10*). Painful ulcerative stomatitis results, often without the telltale fever blister as a clue to its infectious cause. The most important systemic consequence of HSV infection is local barrier breakdown, facilitating the entry of commensal oral microorganisms into the circulation, which can lead to sepsis by oral organisms, such as alpha-hemolytic streptococci, as discussed below. In intensively treated leukemia and bone marrow transplant patients, HSV can also spread to other organs, resulting in esophagitis, tracheitis, pneumonitis, or widely disseminated disease. Before acyclovir was available, 5%–10% of HSV-infected patients undergoing bone marrow transplantation died.

This infectious cause of oral mucositis is frequently indistinguishable from noninfectious (toxic) mucositis caused by chemotherapy or radiotherapy. For example, oral mucositis was reported to be the dose-limiting toxic effect for etoposide, an epipodophyllotoxin congener that has assumed an important role in the treatment of lymphomas, leukemia, and testicular and small cell lung cancers. When phase I dose escalation studies of etoposide were repeated with acyclovir prophylaxis to prevent HSV reactivation, the maximally tolerated dose of etoposide was not achieved, even at 50% higher doses (*11*). Ulcerative mucositis is still seen after administration of etopo-

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Table 1. Types of systemic consequences from mucositis

Pain and discomfort
Impaired hydration
Impaired nutrition
Systemic infection
Indicator of other organ toxicity

side with acyclovir prophylaxis, especially at high etoposide doses, but it is less severe. It is clear that much of the ulcerative mucositis formerly attributed to tissue damage from cytotoxic agents is instead due to reactivation of HSV. This distinction is of utmost clinical importance, because HSV-associated mucositis is amenable to antiviral therapy.

The frequency of HSV reactivation in cancer patients has been best studied in intensively treated patients, such as leukemia and bone marrow transplantation (BMT) patients. In these groups, reactivation occurs in 70%–80% of HSV-seropositive patients (*10,12,13*), and the morbidity of infection is considerable. Unfortunately, the frequency of HSV reactivation and the morbidity of infection have not been well studied in less intensively treated cancer patients.

Acyclovir offers effective control of HSV infection, whether administered prophylactically (*12–15*) or therapeutically (*16–19*). The pros and cons of antiviral prophylaxis have been discussed (*20,21*). Clearly, the optimal strategy (prevention or treatment) for control of HSV infections must be individualized for different groups of patients, taking into consideration the frequency of reactivation, the severity of immunodeficiency, the morbidity of HSV infection in that patient population, the effectiveness of the strategy, and a consideration of how likely the strategy is to lead to the emergence of antiviral resistance.

Bacterial Infections

Bacterial infections are of less significance today than in the past, perhaps because of the routine use of systemic broad-spectrum antibiotics given empirically at the first sign of fever in neutropenic patients. Nevertheless, studies have found that between 25% and 54% of cases of septicemia in neutropenic cancer patients appear to originate from oral infection (*4*).

While gram-negative bacteria have been the most problematic, in recent years a number of cancer centers have noted alpha-streptococcal bacteremia in intensively treated patients (*22–25*). *Streptococcus mitis* has been the most common species found. In some patients, a life-threatening shock syndrome has accompanied the sepsis, with death frequently ensuing despite aggressive antibiotic treatment (*25*). In our center, this syndrome has occurred only in patients with antecedent oral mucositis. Three reports have implicated oral mucositis as a major risk factor (table 3).

Table 2. Major oral infections and their relative significance locally and systemically

	Significance[a]	
Agent	Local	Systemic
HSV	+++	+
Streptococci	+	+++
Candida species	++	+++

[a]Rated from least (+) to most (+++) significant.

In one report (*22*), during an 18-month period at the Hammersmith Hospital, 10 episodes of sepsis caused by viridans streptococci occurred during neutropenia in 93 patients (14%), 42 patients treated for acute leukemia or chronic myelogenous leukemia (CML) in blast crisis and 51 patients who underwent BMT for CML in chronic-phase or severe aplastic anemia. Seven of the 10 infections were due to *Streptococcus mitis*. All 10 infections occurred in the 42 patients (24%) treated for acute leukemia or CML in blast crisis. Seven of the 10 patients with sepsis had signs or symptoms of oral ulceration. Noting that *Streptococcus mitis* is primarily an inhabitant of the buccal mucosa, the authors speculated that oral ulcerations induced by the intensive chemotherapy regimen caused a breach in the oral surface, allowing bacteria to invade the bloodstream. It was implied that the cytotoxic regimen given to the nontransplant leukemia patients was more toxic to the oral mucosa than the regimen used for the BMT patients. An alternative, less-favored explanation for the high incidence of streptococcal sepsis was the use of Hickman catheters, allowing a breach in the integument. Unfortunately, the frequency of oral mucositis (and the use of Hickman catheters) in patients with and without streptococcal sepsis was not reported.

In a second report, 60 consecutive BMT patients were studied at the Karolinska Institute over a 4-year period (*23*). Eight of the first group of 30 patients (27%) developed viridans streptococcal sepsis. In contrast, in a second group of 30 patients, none developed streptococcal sepsis ($P < .01$). Two differences in supportive care were made for the second group. First, acyclovir was used either to prevent or to treat HSV infection. Second, a randomized trial comparing cyclosporine and methotrexate as prophylaxis for graft-versus-host disease was under way. The authors conclude that the reduction in streptococcal sepsis was due to less oral ulceration. Although it was acknowledged that the improvement could be due to the substitution of cyclosporine for methotrexate, the preferred reason offered was better control of HSV infection by acyclovir, since even patients given methotrexate did not develop streptococcal sepsis after the introduction of acyclovir.

In a third report, Bostrom and Weisdorf noted a correlation between radiation dose to the oral cavity in BMT patients and the frequency of viridans streptococcal sepsis (*24*). Streptococcal sepsis occurred in three of 32 patients (9%) who received <60 cGy, 12 of 65 patients (18%) given 750 cGy, and nine of 23 patients (39%) given 1,320 cGy ($P < .05$). Their data did not support an association between HSV infection and streptococcal sepsis, but the much lower incidence of HSV infection (20%) than in most BMT groups raises questions about the adequacy of viral surveillance or some other unique feature about this group of patients (such as a very low incidence of HSV seropositivity).

In a fourth report (*25*), 131 of 821 BMT patients (16%) developed viridans streptococcal sepsis between 1976 and 1987. Ten patients developed cardiorespiratory collapse with sepsis, and six died despite aggressive multiagent antibiotic therapy. Since the institution of vancomycin prophylaxis, none of 83 patients receiving transplants in 1988 developed streptococcal shock. Unfortunately, whether the 1988 experience (0 of 83) is a significant improvement over the previous experience [10 of 821 (1%)] remains unsettled.

Table 3. Suspected role of oral mucositis in viridans streptococcal sepsis in chemotherapy-treated patients

Report (ref. No.)	Patient group (No.)	No. (%) with viridans streptococcal sepsis	Suspected risk factor
Cohen et al. (*22*)	Acute leukemia and BMT (93)	10 (14)	Oral mucositis due to chemotherapy
Ringden et al. (*23*)	BMT (60)	8 (13)	Oral mucositis from HSV
Bostrom and Weisdorf (*24*)	BMT (110)	24 (22)	Oral mucositis from radiotherapy
Steiner et al. (*25*)	BMT (821)	131 (16)	Intensive cytotoxic treatment[a]

[a] Oral mucositis was not specifically evaluated as a risk factor.

In each of the above reports, different strategies were suggested to approach the problem. One group controlled the streptococcal sepsis by reducing mucositis via control of HSV infection (*23*). Another group suggested that addition of vancomycin to the initial empiric antibiotic regimen for neutropenic fever be considered (*22*). Antibiotic prophylaxis was being explored by a third group (*25*).

While each of the above studies had methodologic shortcomings, they support the concept that oral mucosal ulceration offers a portal of entry to the systemic circulation for commensal oral bacteria. These oral ulcerations may be caused by chemotherapy, HSV infection, radiotherapy, or some combination of these factors.

In view of the varying experiences reported from different centers as to the possible etiology of the mucositis, it is clear that each institution should evaluate the scope of its own problem with streptococcal sepsis and attempt to understand its cause, given different patient characteristics and treatments between centers. Then, reasoned strategies to design the best management can be developed to meet each center's needs.

Fungal Infections

Fungal infections are frequent and usually due to *Candida* species, which are commensal organisms residing on oral and gastrointestinal mucosal surfaces. While local *Candida* infections of the oral mucosa can be painful, the most serious consequence is spread to the esophagus or systemic dissemination. At present, systemic fungal infection is the most common cause of infectious death in neutropenic cancer patients, because established systemic infections are difficult to recognize and respond poorly to treatment (*26–28*). Recent studies at our institution emphasize the importance of the mucosa as a host defense against systemic *Candida* infection in neutropenic cancer patients.

Candida tropicalis is a more common systemic pathogen than *C. albicans* in neutropenic cancer patients, despite being a less frequent colonizer of mucosal surfaces (*26,29*). Among 89 consecutive patients treated intensively for leukemia or undergoing BMT at our center over a 12-month period, we observed 18 episodes of *Candida* sepsis in 17 patients (19%) (*26*). Fifteen of the 18 infections (83%) were caused by *C. tropicalis*, and three were due to *C. albicans*. Other centers subsequently also reported *C. tropicalis* as a more common systemic pathogen than *C. albicans* in intensively treated cancer patients (*30,31*). In contrast to the greater frequency of *C. tropicalis* infection, only 25 patients (28%) were colonized by *C. tropicalis* (*26,29*), whereas 60 patients (67%) were colonized by *C. albicans*. Stated otherwise, only three of 60 (5%) patients colonized by *C. albicans* became infected, but 14 of 25 (56%) patients colonized by *C. tropicalis* became infected ($P < .001$) (table 4). These data suggested that there was a difference in virulence between the two *Candida* species.

Experiments in animals were undertaken to examine the virulence and the role of the portal of entry of the *Candida* organisms. Groups of mice were given increasing doses of *C. albicans* or *C. tropicalis* intravenously to establish the dose required to kill 50% of the animals (LD_{50}) (*32*). The LD_{50}'s of *C. albicans* and *C. tropicalis* were comparable (table 5). We next considered the possibility that the organisms isolated from patients at our center may differ from those isolated at other cancer centers. Thus, we tested the virulence of paired isolates of both *Candida* species from several cancer centers in mice (*33*). Again, we found that the LD_{50} of both *Candida* species was similar regardless of the cancer center where they were isolated. These results were consistent with those reported earlier for similar animal models. Next, we tested the virulence in mice immunocompromised by administration of cytarabine to produce neutropenia. The LD_{50} was reduced more than 100-fold when the mice were conditioned with cytarabine, but the LD_{50} was still equivalent for the two *Candida* species (table 5).

Since these experiments did not explain the difference in virulence between *C. albicans* and *C. tropicalis* seen in the clinical setting, we decided to explore whether the portal of entry was an important determinant of infection. Accordingly, the design was modified to allow delivery of the organisms to the mucosal surface rather than into the circulation. The *Candida* organisms were administered orally in a slurry via a Teflon catheter into the esophagus in graded doses. Animals were sacrificed 72 hours after inoculation, and sections of liver, lungs, and kidney were cultured to ascertain whether systemic dissemination had occurred (*32,33*). Control experiments demonstrated that administration of yeast cells alone, even in the

Table 4. Episodes of *Candida* sepsis and colonization in 89 intensively treated patients with leukemia or undergoing bone marrow transplantation[a]

Species	No. (%) of 89 patients	
	Colonization	Sepsis
C. albicans	60 (67)	3 (3)
C. tropicalis	25 (28)	14[b] (16)

[a] Data are from references *26* and *29*.
[b] Fifteen infections occurred in 14 patients.

Table 5. Experimental *Candida* infection in mice[a]

Route of inoculation	Species	Conditioning		Disseminated infection[b]
		Cytarabine	Gentamicin	
Intravenous	*C. albicans*	No	No	+
	C. tropicalis	No	No	+
	C. albicans	Yes	No	++++
	C. tropicalis	Yes	No	++++
Oral	*C. albicans*	No	No	0
	C. tropicalis	No	No	0
	C. albicans	No	Yes	0
	C. tropicalis	No	Yes	0
	C. albicans	Yes	No	—[c]
	C. tropicalis	Yes	No	—[c]
	C. albicans	Yes	Yes	++
	C. tropicalis	Yes	Yes	++++[d]

[a] Mice were given graded doses of *C. albicans* or *C. tropicalis* intravenously or orally after being conditioned with cytarabine, gentamicin, or both. Data are from references *33* and *34*.

[b] The number of symbols indicates the relative ease with which lethal or disseminated infection could be produced, from least (+) to greatest (++++), while a 0 indicates no cases of disseminated infection.

[c] Animals died from bacterial sepsis.

[d] Disseminated infections were routinely established with 10-100-fold-smaller *C. tropicalis* than *C. albicans* inocula.

highest doses possible, did not establish infection. Further control experiments in which mice were conditioned with either cytarabine (to produce neutropenia and mucosal damage) or gentamicin (to suppress endogenous bacterial flora and permit fungal overgrowth) did not produce infection. However, when mice were given *Candida* organisms after being conditioned with cytarabine and gentamicin (to simulate the clinical situation), disseminated infection by both *Candida* species could be produced. Graded doses of organisms were given to groups of animals to establish the dose required to infect 50% of the animals (ID_{50}). Paired isolates (the same ones used in the intravenous inoculation experiments) from our center and other cancer centers were tested. Disseminated infection occurred with all isolates after cytotoxic and antibiotic conditioning. The ID_{50} for all *C. tropicalis* isolates was consistently lower than the ID_{50} for *C. albicans* isolates by greater than 10- to 100-fold (*33*) (table 5).

Clearly, the difference in virulence of *C. albicans* and *C. tropicalis* in the neutropenic host conditioned by cytotoxic therapy (which damages the mucosa) and antibiotics (which suppress bacteria) occurred only when the mucosal surface was the portal of entry and its integrity was damaged.

We conclude that events at the mucosal level appear to explain the observation that *C. tropicalis* is more virulent in the neutropenic host than *C. albicans*. What early factors at the mucosa are pertinent to fungal pathogenesis is unknown. Possible determinants include differential growth at the mucosal surface, differences in adherence, and differences in penetration due to yeast virulence factors.

Treatment of established systemic *Candida* infection has had poor results, emphasizing prevention of infection in high-risk patients with prolonged neutropenia. Oral nystatin, amphotericin B, and miconazole treatments have had minimal efficacy. Oral ketoconazole has been found to be effective in prevention of mucosal infections, but trials to date have not clearly shown significant reduction in systemic infections. In contrast, prophylaxis with intravenous miconazole (*34*) and intravenous amphotericin B (*27*) have both been effective in reducing systemic *Candida* infection, and either agent should be strongly considered in high-risk intensively treated patients when prolonged neutropenia is expected.

TOXIC EFFECTS IN OTHER ORGANS

We recently recognized that noninfectious oral mucositis can be used as a marker of toxic effects in other organs (Wingard JR, Niehaus CS, Peterson DE, et al: submitted). Hepatic veno-occlusive disease (HVOD) is a frequent life-threatening organ toxic effect caused by intensive cytoreductive therapy (*35*). We found that in a group of 47 prospectively studied BMT patients, 17 patients (34%) developed ulcerative oral mucositis and seven patients (15%) developed HVOD. Six of the seven patients who developed HVOD had oral mucositis. The onset of mucositis occurred a median of 14 days earlier than the onset of HVOD. In a time-dependent analysis, patients who developed oral mucositis had a 6.5-fold greater risk of developing HVOD than did patients without mucositis. Thus, patients who develop oral mucositis may be a subgroup of patients in which investigative therapies to prevent HVOD can be tested. Studies are under way at our center to look for a correlation between mucositis and drug concentrations in serum and saliva.

In another study at our center, we observed a strong association between HVOD and interstitial pneumonitis (*36*). Presently, we are examining the association of mucositis with both HVOD and interstitial pneumonitis in a larger cohort of patients. The ready accessibility of the oral mucosa for examination and biopsy would permit surrogate evaluation of toxicity to other epithelial tissues with which the association of toxic effects is strong.

At our center, we have begun a dose adjustment study of busulfan, used in our BMT preparation regimen, based on measurements of serum drug concentrations. Previous data showed that patients whose drug levels in serum were in a high range were at great risk for life-threatening toxicity (HVOD) (*37*). We will measure blood concentrations after the first dose and adjust subsequent doses. Patients with high serum levels will have the dose reduced to determine whether the incidence of oral mucositis, HVOD, and interstitial pneumonitis can be reduced. Patients whose serum levels are below this high-risk range will have subsequent doses increased to achieve serum concentrations just below the high-risk range, so as to increase the antitumor effect. Studies such as this, if successful, should permit more intelligent dosing to achieve better tumor control while minimizing the risks of toxicity.

UNANSWERED QUESTIONS

A number of questions remain to be answered and strategies need to be developed for management of oral complications. We still have a relatively poor understanding of why some treatments cause a greater degree of mucositis than others. Are there differences in drug delivery to the oral mucosa or differences in susceptibility of the oral mucosa to different drugs? Can we modify our treatment regimens to achieve greater therapeutic ratios, to reduce the toxicity to the mucosa while optimizing the antitumor effect?

Although we now recognize the role of infection in many oral complications and have developed antimicrobial strategies to prevent some of these, we still have a relatively poor understanding of the complex interaction of infectious pathogens and the oral cavity as a host defense. We need to better understand the early steps in pathogenesis of infections at the mucosal barrier.

Finally, we are just beginning to use the oral cavity as a window to detect, perhaps predict, systemic organ toxicities. We should exploit this potential more fully.

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II. Pretreatment Assessment

Pretreatment Oral Assessment

Stephen T. Sonis,* Phillip D. Woods, B. Alexander White

Individuals undergoing cancer therapy may be at risk for a wide variety of oral problems that can significantly affect morbidity and mortality. Pretreatment oral assessment of these patients is an opportunity to identify and eliminate potential sources of sepsis and irritation. While preliminary studies strongly support the efficacy of pretreatment oral screening programs, a number of issues have yet to be addressed relative to patient-related and cost-related outcomes. Such studies should provide specific data regarding the focus of oral screening for specific malignancies, forms of cancer therapy, and oral pathology. As the aggressiveness of cancer therapy increases, comprehensive oral evaluation with clinical, radiographic, and adjunctive components before treatment is warranted. [NCI Monogr 9:29–32, 1990]

Individuals undergoing cancer therapy are at risk for a wide variety of oral problems that can significantly affect morbidity and mortality (*1*). For patients who receive chemotherapy, problems related to the mouth fall into two major groups, local and systemic. Mucositis and sepsis are the best-known examples of these respective groups. Patients who receive irradiation to the head and neck are more likely to have problems localized to or around the site of therapy. Fortunately, our approach to these patients' oral problems has shifted from damage control to aggressive prospective and pretreatment care and follow-up. This approach to comprehensive oral management at the Brigham and Women's Hospital and the Dana Farber Cancer Institute significantly reduced the frequency of oral problems, from 40% to about 12% (*1,2*). Implicit in any prospective approach is the identification and elimination of potential problem sources before treatment.

RATIONALE FOR PRETREATMENT ASSESSMENT

Myelosuppressive Chemotherapy or Radiation

Patients who are about to undergo myelosuppressive therapy are at major risk for sepsis, which in fact is the major cause of death in these individuals (*3*). In addition, the patient's reduced ability to fend off infection is coupled to the loss of oral epithelial integrity as a consequence of the direct stomatotoxic effects of many chemotherapeutic agents (*4*).

Thus, the objectives of a screening program for this group of patients should include (*a*) identification of sites of asymptomatic oral infection or potential oral infection and (*b*) identification of sources and sites of chronic irritation.

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Treatment for Head and Neck Cancer

The concerns of pretreatment oral evaluation for this patient group differ from those for the patients discussed above. For most patients, treatment will consist of local therapy in the form of surgery or radiation, or both, although chemotherapy is now being included more often (*5*). The objectives of pretreatment screening in this group are (*a*) identification of possible sources and sites of osteoradionecrosis, (*b*) presurgical assessment for prosthetic rehabilitation, and (*c*) initiation of a preventive protocol for radiation-induced caries.

EFFECTIVENESS OF SCREENING

In many ways we have been presumptive in assuming that pretreatment oral screening is the rational approach to oral care in the cancer patient. However, a number of critical questions and issues must be addressed before an ideal screening program can be determined. First, it is incumbent on us to demonstrate, in a nonanecdotal way, that screening does in fact favorably influence patient outcome. Second, we must demonstrate that screening and subsequent treatment are cost effective in the prevention of sequelae versus not screening. Third, we need to determine which oral conditions are best screened and which patients are most likely to have significant outcome changes because of screening.

We have only recently started to accumulate the data needed to answer these questions. In a recently reported study, our group evaluated the type and frequency of potential oral sources of infection in patients about to undergo bone marrow transplant for treatment of malignancies (*6*).

Of the 95 patients evaluated, 72% were found to have at least one of the following: American Dental Association type III or IV periodontal disease, asymptomatic periapical disease, faulty restorations, problems associated with third molars, or ill-fitting prostheses.

While the incidence of pathology probably differs little from that in normal populations, we suppose that the consequence of nontreatment is much more significant for the patient undergoing cancer therapy. The question arises whether this assumption is correct and whether the risk of nontreatment is equivalent for all diagnoses. Clearly, for a screening program to be worthwhile, it must precipitate treatment intervention that favorably modifies the patient's cancer therapy outcome.

In order to assess screening efficacy, we can measure patient-related outcomes such as quality-adjusted life-years, life expectancy, additional days of hospitalization, febrile days, number of oral complications, and death. Alternatively, or more likely concurrently, we also need to address the cost effectiveness of an oral screening program. Sound quantitative data for both outcome measures are sparse, especially for the patient with non-head and neck malignancies. However, we are now developing a broader, analyzable data base.

As early as 1982, Greenberg and associates (7) suggested that infection around third molars (pericornitis) was a significant source of sepsis in patients undergoing therapy for acute leukemia. Importantly, they also found that pre-cancer therapy intervention for this problem had a significant impact on outcome. We decided to study this single diagnosis further relative to a cost analysis for screening and pre-cancer therapy oral treatment (fig. 1). The frequency of positive findings in our analysis is based on data from the study of Woods and Sonis (6) and data obtained from a pool of 250 patients who underwent bone marrow transplantation or induction chemotherapy at our institution. Of the patients in the latter category, a number were so acutely sick with their malignancy that dental intervention prior to the start of chemotherapy was inappropriate. We followed the development of oral complications related to third molars in this group.

In our analysis (fig 1), we begin with a hypothetical patient base of 200 who will undergo intensive, noninductive chemotherapy for acute leukemia that results in significant and prolonged myelosuppression (wbc count <1,000 for 5 or more days). One hundred patients are screened for potential third-molar pathology and 100 are not screened. Of the screened patients, 26 will be positive and all 26 will have the third molar(s) extracted. We presume 100% efficacy in complication prevention if the tooth or teeth are removed, and hence there are no oral complications in this category.

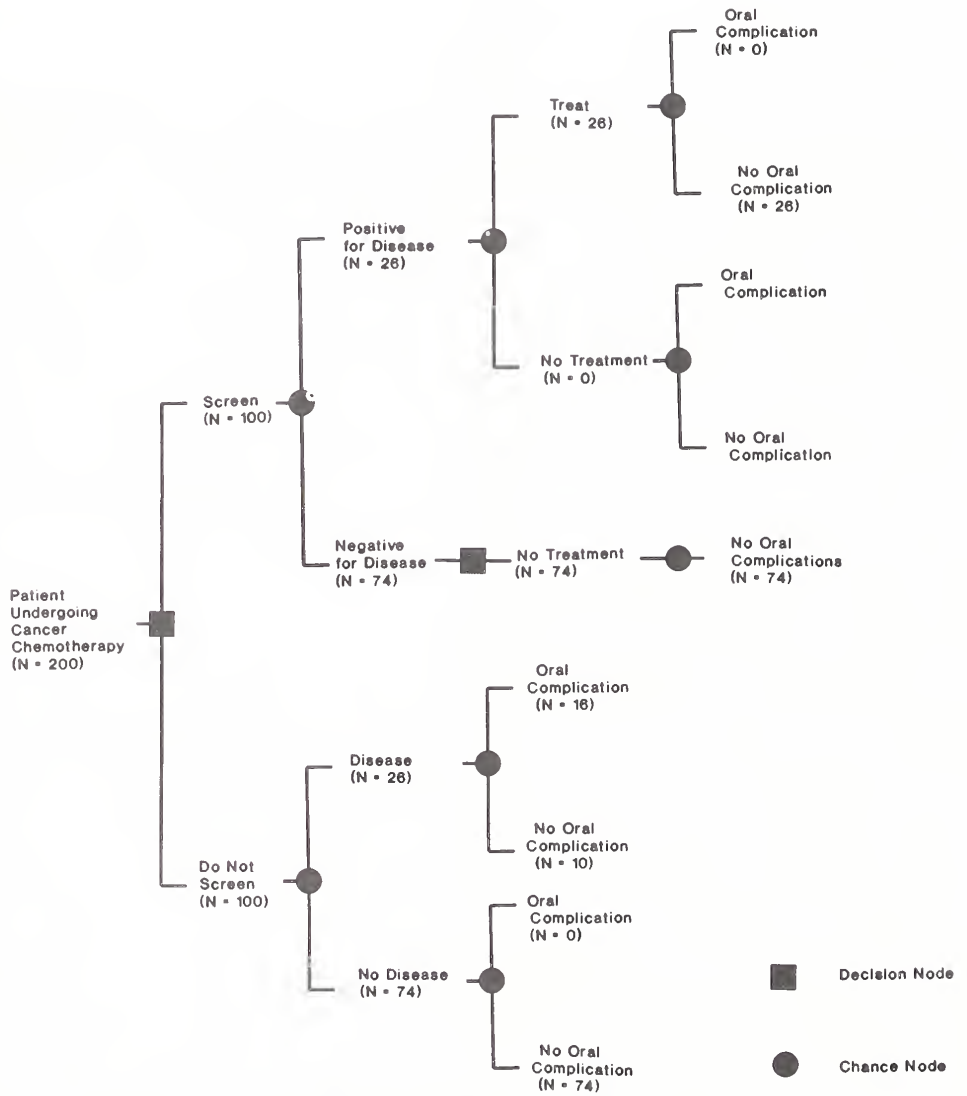

Figure 1. Decision tree and cost analysis of third-molar-related pathology for 200 patients undergoing cancer chemotherapy for acute leukemia. One hundred patients are screened, and 100 are not. Twenty-six percent of all patients will have pathology related to third molars. Of the patients whose third molars are not treated, 60% will go on to develop infection during myelosuppressive therapy.

Of the 100 patients who are not screened, 26 will have undetected third-molar-related disease. Assuming that our patient-based data are accurate, 60% or 16 of these patients will then go on to develop oral complications, often resulting in sepsis.

Except for data on the frequency of oral complications, we still lack data relative to patient-related outcomes. However, the cost analysis of screening for this single source of potential infection is interesting. We compared the costs of the screening program with the costs for patients not screened. We assumed the total cost to be the cost of screening plus the cost of treatment of patients with positive findings.

We assumed that the postoperative morbidity associated with treatment was negligible (0). Therefore, the cost of the screening program for the 100 patients was: Cost of screening (100 patients × $120) + cost of treatment (26 patients × $200) = $17,200 total cost.

We then calculated the cost of managing complications for the nonscreened patients. We assumed that patients had completed induction therapy and were being treated on an ambulatory basis until requiring hospitalization for treatment of sepsis as follows: Cost per hospitalization day ($2,342) × average stay for febrile neutropenic patient (7 days) × 16 patients = $262,304 total cost.

The difference in costs associated with the consequences of screening versus not screening for potential third-molar pathology is dramatic. Had the 100 patients who were not screened received prechemotherapy oral assessment and treatment, the potential savings would have been $245,104.

While the magnitude of this difference is maximized by the presumption that sepsis prevention maintained the outpatient status of the study group, it seems likely that such a dramatic difference would result in some cost savings under almost any circumstances imaginable. More concrete data are needed to support or refute this hypothesis.

We must now ask whether screening for all forms of oral pathology would offer as significant an outcome as screening for third-molar pathology. Woods and Sonis (*6*) found that periodontal disease was the most consistent positive finding in the patients evaluated. While it has been well established that acute periodontal infection may be a significant source of sepsis in myelosuppressed patients (*8*), Peterson (*9*) notes that "the degree of periodontal disease present prior to admission does not appear to correlate with the frequency of acute periodontal infection." Thus, spending significant resources to screen for periodontal disease may not be worthwhile. It seems probable that eliminating sources of oral irritation before cancer therapy is beneficial. However, no substantive data exist to substantiate either of these presumptions.

While the efficacy of screening in patients about to receive head and neck radiation is relatively well documented (*10*), we need to accumulate data on the effectiveness of intervention for periodontal disease, asymptomatic periapical disease, and defective restorations for patients about to undergo chemotherapy. Furthermore, we need to link this analysis with other patient variables, including age, diagnosis, and projected cancer treatment plan.

Some factors seem to predispose patients to the oral complications associated with cancer therapy. Identification and definition of these risks could lead to identification of target populations for screening. Among the factors to be considered in risk assessment are degree and duration of expected myelosuppression, cancer diagnosis, form of anticipated cancer therapy, patient age, prior oral or dental disease, and level of oral problems anticipated during therapy.

TIMING OF ASSESSMENT

If oral screening is performed so close to the initiation of cancer therapy as to preclude dental intervention, the value of the screening program is limited. To maximize the impact of screening, adequate time for treatment and healing must be allowed. For the patient about to receive head and neck radiation, 2 weeks should be planned. For the patient about to receive myeloablative therapy, a similar amount of time is desirable because the wbc count nadir should occur about 12–14 days following the initiation of chemotherapy.

A patient's clinical condition may preclude ideal timing of oral screening and treatment. In these instances, oral screening should be performed as soon as possible after tumor diagnosis; the results may be used first as a baseline and then as the basis for a dental treatment plan. For example, suppose a patient with leukemia in blast crisis is started on an inductive chemotherapy regimen immediately following diagnosis. The patient would be screened, and positive oral findings would be noted. Should the patient develop sepsis during induction, a potential oral source might have already been noted. More importantly, if active oral infection was present, the antibiotic regimen might be modified. Following bone marrow recovery, the sources of oral findings would be eliminated.

COMPONENTS OF COMPREHENSIVE PRETREATMENT ASSESSMENT

History. Both medical and dental histories should be obtained. The patient should be asked specifically about the frequency and extent of past dental care, the age and condition of existing prostheses, oral soft tissue lesions (including traumatic lesions, candidiasis, and herpes simplex infection), oral symptoms (including periodontal or tooth pain or sensitivity), gingival bleeding or swelling, pericornitis, and salivary gland function.

Consultation. It is frequently beneficial to consult the patient's former or present dentist to confirm earlier treatment, assess ongoing dental therapy, and discuss other aspects of the patient's dental health. It is often helpful to obtain past dental radiographs for comparison. Consultation with the physician responsible for the patient's cancer therapy as to the timing, modality, and specifics of therapy is essential both for risk assessment and to plan any required dental treatment.

Clinical examination. A comprehensive clinical evaluation performed in an appropriate setting should include the following: (*a*) extraoral soft tissue examination of the head and neck; (*b*) intraoral soft tissue examination; (*c*) periodontal screening examination, including tooth mobility, gingival inflammation, loss of gingival attachment and alveolar bone, suppuration, and oral hygiene level; and (*d*) dental evaluation, including prostheses or orthodontic appliances, percussion sensitivity, tooth vitality, defective restorations, caries, broken or fractured teeth, and partially erupted teeth, particularly third molars.

Radiographic examination. Radiographic evaluation should ideally include the following: (*a*) periapical radiographic evaluation (full mouth series or panoramic radiograph); (*b*)

interproximal areas (bitewings); and (*c*) supplemental films and imaging studies as needed (i.e., sinus films, magnetic resonance imaging, computed tomography). Information of importance in radiographs, including latent or dormant dental infection, periodontal disease, partially erupted or impacted teeth, intrabone pathology (i.e., cysts, granulomas, metastases), and foreign bodies, should be noted.

Laboratory data. Laboratory data are an adjunct to clinical and radiographic data and serve two major functions relative to pretreatment assessment. First, the data may be used to confirm a dental diagnosis, as in the case of bacterial analysis for the patient with periodontal disease; second, it may provide information about the patient's systemic status, which could influence the patient's ability to receive dental care.

CONCLUSION

Pretreatment oral assessment for patients about to undergo cancer therapy may significantly reduce sepsis and other complications associated with oral disease. However, a number of questions about patient-related and cost-related outcomes need to be addressed to ascertain the true value of screening services. Such studies should also provide data on the focus of oral screening for specific malignancies, forms of cancer therapy, and oral pathology. As the aggressiveness of cancer treatment increases, it is likely that a well-aimed oral screening program will increase the well-being of patients and the cost-effective use of health care services.

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Essential Aspects of a Pretreatment Oral Examination

Peter Stevenson-Moore

Certain disease entities or their management impose conditions that heighten risks of oral complications or systemic complications of oral origin. The pretreatment oral examination attempts to identify the main factors that will cause risk so that steps may be taken to control or eliminate as many as practical before treatment is begun. Additional tests may be indicated to provide more detailed information on which to base clinical diagnoses and oral therapy. NCI Monogr 9:33–36, 1990]

The pretreatment oral examination is an essential element in the preparation of cancer patients who require treatment that impinges upon the oral cavity or related structures. This includes patients undergoing radiation therapy or surgery to the head and neck; neutropenic patients; and patients who are immunosuppressed as the result of therapy. Failure to adequately assess the pretreatment status of the soft and hard oral tissues and to take appropriate precautions can result in complications that may limit the delivery of cancer therapy. Failure to anticipate long-term posttreatment complications can lead to severe and irreversible changes that compromise the quality of life. In a litigious society, failure to provide warning of impending complications, failure to provide for appropriate preventive measures, and failure to undertake strategies that will enhance the quality of life may all be considered forms of malpractice.

Consideration of the essential aspects of the pretreatment oral examination requires that each observation made have a specific influence upon the management of the patient. In addition, it is important that the recommendations for the pretreatment examination not be confused with the requirements for an oral cancer examination, which should be a routine feature of the general dental examination. The assumption is made in this article that the true extent of the cancer to be treated has been properly assessed.

Among the many tests that are available are several that may be indicated for use only under specific conditions. Consideration of these components of a complete oral examination is also excluded from this discussion, as they are not essential to the pretreatment oral examination.

OBJECTIVES

The pretreatment oral examination has three objectives: to establish baseline data, and to develop treatment strategies that avoid complications both during and after cancer therapy.

Baseline Data

A complete pretreatment record is essential, not only for the planning of pre-cancer therapy dental care, but also for posttherapy follow-up. The prevention of many complications is dependent upon pretherapy intervention, while the timely interception of late complications will depend upon an ability to compare the existing oral status with the pretherapy status. Proper epidemiologic evaluation of the success of dental intervention is only possible with complete pre- and posttherapy data.

Several record forms are in common use and are adequate as far as they go. The standard dental charts include a tooth count; a diagrammatic representation of decayed, missing, and filled surfaces; a record of pocket depths, gingival recession, furcation involvements, and tooth mobilities; sensitivity to percussion; tooth vitality; bleeding indices; and attached mucosa. Forms do not capture a good description of the appearance, contour, or consistency of soft tissues. Photographs are useful but are often hard to standardize owing to variations in access to the mouth, illumination, emulsion, and technique. However, one can appreciate the advantages that offset the limitations of the technique. Initial studies have been undertaken at my and others' institutions to develop a more ideal tool (*1,2*). I am unaware of any that has received wide approval.

Complications During Therapy

A complete pretreatment oral assessment will permit the development of strategies that avoid treatment complications during cancer therapy that are life threatening, that might force treatment to be stopped, that would be dose limiting, or that diminish the quality of life. These problems include pathologic overgrowth of commensal organisms, colonization of pathogenic organisms, increased tissue fragility and ulceration, and reactivation of latent infection or chronic infection. These points will not be discussed here.

Complications After Therapy

A complete pretreatment oral assessment will permit the development of strategies that reduce or avoid treatment complications following cancer therapy, such as osteoradionecrosis, caries, xerostomia, graft-versus-host disease, and chronic mucosal infections.

There are two aspects to this problem, which may be viewed as horizontal and vertical in nature. The horizontal aspect refers to the development of strategies for the ongoing management of the individual patient that must be initiated immediately. Some estimation must be made of the risk to which the individual will be exposed by the type of treatment he will receive and by factors predisposing him to a variety of potential difficulties. The vertical aspect of the problem refers to ongoing study of repeated examinations that yield information from which conclusions can be drawn about the incidence of complications. Long-term studies of complications are difficult to complete because of the loss of patients resulting from the very nature of the diseases from which they suffer, but such studies must be undertaken if we are to have hard data to substantiate the claims

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that we make about the need for ongoing dental supervision. If both short- and long-term benefits cannot be demonstrated for each of the interventions that we recommend, then there should be no intervention, and no health system should be required to pay for them, except on an experimental basis.

The financial implications of failure to diagnose preexisting complications and to recognize accelerated treatment-related oral deterioration are considerable. The ability to distinguish between problems that result from treatment, those that existed before treatment, and those that result from neglect can be critical in determining the responsibility for the provision of care and for cost, particularly when such cancer- or treatment-related dental care is an insured benefit.

ESSENTIAL DATA

Consideration of the essential aspects of the pretreatment examination cannot be separated from the necessary planning for follow-up examinations. In order to satisfy the objectives of the pretreatment examination, the following data must be obtained: cancer diagnosis; medical history; dental history; and dental charting, including presence or absence of teeth and restorations and an assessment of their status, tooth mobilities, percussion sensitivities, demineralization, and caries.

Dental Charting

The chart on which these recordings are made is not important as long as all of the observations are made and are readily understood by all personnel using the chart and the chart is available for follow-up purposes. A fresh chart should be made at the time of any subsequent examination, as it is vital that the information obtained from an examination not be lost or camouflaged. When changes in dental status are slight, there has been a tendency for minor updates to be made to existing diagrams. This is disastrous for future follow-up purposes.

Periodontal Charting

Periodontal charting data should include pocket depths, gingival recession, inflammation, suppuration, and an oral hygiene assessment. The decisions resulting from these observations will depend upon a variety of disease-, treatment-, and host-related factors. Whereas suppuration of a gingival margin may argue for removal of the offending tooth, this might not be urgent if it is outside the field of radiation for squamous cell carcinoma, while it might be of the greatest urgency to remove the tooth before the onset of immunosuppression associated with bone marrow transplantation. There may also be an opportunity to control such a situation in some patients before there is higher tissue risk resulting from treatment-related changes in the oral environment.

Volumetric Assessment of Saliva

The assessment of saliva volume has been an area of considerable interest over the last several years. The difference between the subjective evaluation made by the patient and the objective evaluation obtained by measurement is often dramatic. Thus, it is inappropriate to rely on the report of the patient. Many methods are available for the measurement of saliva volume; they range from the placement of vacuum-retained canulas to the use of a dry tongue blade used like an engine's oil dipstick. The former is too time-consuming and intricate, while the latter fails to provide a quantifiable result and can be traumatic when the oral mucosa already shows marked fragility. As a result, the simpler, if slightly inexact, method of saliva collection by expectoration into a graduated centrifuge tube is preferred. This collection receptacle is favored because the measurement of volume is quickly assessed visually and, in the event of significant foam volumes being collected, allows immediate reduction to liquid by centrifugation in a laboratory centrifuge. If one is not available, volume of foam collected is recorded. Results are recorded in milliliters per minute (*3*).

Values for normal and abnormal salivary flow have not been formally agreed on, but the ranges shown in table 1 should be acceptable to many involved in this area of investigation. These values have been assembled from a variety of sources and compared with recently published work by Sreebny and Valdini (*4*). Comparison of the two suggested ranges for normal and abnormal flow indicates some common features. Saliva volume can indicate the urgency with which preventive measures should be introduced and the frequency of follow-up that will be necessary. Comparison of pre- and posttreatment values gives an indication of the degree of change that may be expected in the behavior of the oral environment.

The ranges in table 1 seem to be reasonably close to each other and probably vary because of the differing situations in which they have been derived. Sreebny's figures are derived from populations of patients who reported subjective responses to xerostomia, while other authors have been working principally with patients treated with radiotherapy for oral cancer. Our data derive from a comparison of caries incidence, tooth demineralization, oral flora, and saliva flow but have not been subjected to rigorous statistical analysis. Work should be undertaken to refine these working values so that specific risk categories can be better defined.

The importance of the continued function of the submandibular and sublingual glands is underrated by many who forget the significance of resting flow in maintaining the mineralization of tooth structure. The lubrication of the oral tissues to facilitate speech and mastication cannot be ignored. The lubrication of the tissues not only allows surfaces to slide when in contact, but interferes with the adherence of potentially pathogenic organisms. A recent consensus conference of the American Dental Association Council on Dental Therapeutics dealt with the related topic concerning the effects of products that increase salivation (*5*).

Table 1. Salivary flow rate ranges

Group	Salivary flow (mL/min)		
	Normal	Low normal	Abnormal
CCABC[a] working values			
Resting	>0.5		<0.25
Stimulated	>1.5		<0.6
Sreebny and Valdini (*4*)			
Resting	>0.2	0.1–0.2	<0.1
Stimulated	1.99 ± 1.06		1.08 ± 0.67

[a]CCABC = Cancer Control Agency of British Columbia.

Radiographs

The relevance of radiographs to the oral examination is usually unquestioned. Though there have been heated debates on the cost-benefit ratio of the procedure, most practitioners agree that the morbidity resulting from the procedure is more than offset by the benefit of this aid to treatment planning. There are, however, more limited applications for treatment-planning radiographs in the pretreatment assessment of cancer patients. Incipient decay is of almost no concern, as the management of such lesions affects the medium- and long-term management of the patient much more than it affects short-term patient management. Radiographs may fail to demonstrate change within bone until as much as 3 months following the actual change in its physical integrity. This is a result of the time it takes for an actual change to occur in the mineralization of the bone matrix. This has been particularly apparent to us during the ongoing management of osteoradionecrosis, when change in the continuity of the mandible has been clinically apparent well before the radiographic change is noted. The same is likely to be true for teeth.

The importance of a radiograph is to be able to locate problems that have not been demonstrated during clinical examination. Periodontal disease does not require radiographic evaluation for its identification and assessment. However, the radiograph is invaluable for the assessment of an area that cannot be approached in any other way and for the elucidation of factors that cannot be determined clinically, such as root length, presence of adjacent unerupted teeth, or the presence of periodontal or periapical radiolucency.

Periapical radiolucency has been a matter of some interest to us also. We have identified a number of periapical radiolucencies that have been referred to an endodontic specialist for assessment. Several have mimicked active periapical lesions in appearance but have not been associated with any particular symptoms. We are advised that in the absence of symptoms, it may be unnecessary to provide obturation of the root canal, and indeed, in a retrospective review of a number of patients, we failed to demonstrate the development of any change in condition following radiation therapy that impinged directly on the teeth with a tumoricidal dose. Whether such apparently encapsulated pathologies are capable of remaining dormant in the immunocompromised patient may be of interest. It is not a risk that many practitioners would wish to take, though when time is of the essence, it is probably safer to leave such lesions without treatment and keep them under careful observation.

Study Models

Study models should be made for construction of gel carriers, for construction of surgical prostheses, as a permanent record of the pretreatment dental structures, and as facial moulages. The making of impressions for study models might at first sight seem to represent a form of therapy rather than a form of examination. In my view this procedure serves both purposes. We find that doing the procedure with the pretreatment oral examination is ideal, as this is one time when the dental personnel can be guaranteed contact with the patient, and therefore preventive procedures can be adequately initiated. The need for this adjunct to full occlusal examination is not always present, but as a three-dimensional record of existing oral structures models it is without peer.

Cultures

Cultures should be done only if there is evidence of microbial overgrowth, either generalized or local. We consider that no advantage is to be gained by obtaining pretreatment cultures of the oral environment for every patient. The chance of turning up an unusual and previously unrecognized potentially pathogenic organism prior to treatment does not seem to warrant the time and laboratory expense involved. Similarly, we do not obtain a routine saliva culture for cariogenic organisms prior to treatment, choosing to rely on a good dental history and an inference based on the examination of the teeth. Posttreatment monitoring of changes in the oral flora of the compromised patient is another issue, and the flora certainly requires ongoing monitoring both quantitatively and qualitatively. We do not yet know all the varieties of organism that should be checked, particularly with respect to periodontal disease in several risk groups.

Diet Assessment

Currently available tools for the assessment of diet are largely imperfect and are often topheavy for routine clinical use. Despite this, control of diet remains important for the maintenance of patient health and for control of the oral environment. The use of full dietary interviews or of specific daily dietary histories takes more time than can normally be allowed in a busy dental clinic (Clark DC, Woo G, Silver JG, et al: submitted for publication). The development of questionnaires that focus on specific food frequency instead of specific daily history would seem to be much more practical (*6*). These would be capable of rapid interpretation by ancillary personnel, and would be designed to indicate the need for dietary evaluation in greater depth.

Plaque and Mineralization

Krasse (*3*) demonstrated the need for control of the mineralization of tooth structure, the maintenance of low levels of plaque, and control of dietary intake, in terms of both frequency and content. Clinical assessment of tooth appearance and of tooth hardness is capable of providing information about the degree of mineralization of tooth structure. Plaque levels can be assessed visually. Both of these measures are capable of quantitative assessment to some degree, although neither measure is particularly sensitive. Both measures have received extensive attention in the literature from the standpoints of epidemiological assessments of large populations and for determining gross changes in individuals. There is some suggestion of a need for more sensitive measures to be developed for the monitoring of the individual status of patients.

SUMMARY

Certain disease entities or their management impose conditions that heighten risks of oral complications or of systemic complications with oral origin. The pretreatment oral examination attempts to identify the main factors that will cause risk so that steps may be taken to control or eliminate as many as practical before treatment begins. Additional tests may be indicated to provide more detailed information on which to base clinical diagnoses and oral therapy.

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Surveillance Cultures

Stephen C. Schimpff

Surveillance cultures can be defined as an attempt to take microbiologic inventory, usually for bacteria and fungi, occasionally for viruses, at predetermined times during a patient's clinical course. They are useful in understanding the epidemiology of infection, evaluating techniques of infection prevention, assaying the effectiveness of preventive techniques, and guiding therapeutic decisions when empiric antimicrobial therapy is indicated. As such, they are most frequently used for patients at high risk of infection, such as those with acute leukemia receiving remission induction chemotherapy or bone marrow transplantation therapy. The sites sampled most frequently for surveillance cultures are the nose, oral cavity (pharynx or gingiva), and either the perianum or a stool specimen. Since hospital microbiology laboratories are not designed for the requirements of surveillance culturing, it is essential that such cultures only be obtained following appropriate communication and agreement with the laboratory directors. [NCI Monogr 9:37–42, 1990]

Surveillance cultures are used principally to study the epidemiology of infection and evaluate methods of infection prevention. They may also be used clinically to monitor some infection prevention strategies and to guide decisions on infection therapy (*1*). This article reviews surveillance cultures from the perspectives of epidemiology, prevention, and therapy and gives some examples of knowledge gained in each area and comments on their clinical use. First, it is important to explain how surveillance cultures have been used at the University of Maryland Cancer Center.

METHODS OF DATA ACQUISITION

Investigations were performed at the Baltimore Cancer Research Program (BCRP)–University of Maryland Cancer Center. Nasal, gingival, axillary, rectal (by moistened swabs), and urine (clean catch) specimens were obtained for surveillance cultures when patients were admitted and twice weekly during hospitalization from 48 patients with acute nonlymphocytic leukemia (ANLL) admitted to the BCRP between July 1, 1969, and December 31, 1971, for induction chemotherapy.

Between 1971 and 1976, 135 (of 166) newly diagnosed patients with ANLL admitted to the BCRP had two sets of baseline cultures of nasal, gingival, axillary, and rectal specimens done on admission. Eighty of these 135 patients had two sets of baseline cultures done on admission plus twice-weekly surveillance cultures of the same sites for a minimal 6-month follow-up (*2*). Ninety-seven of these 135 patients had two sets of baseline cultures taken on admission plus follow-up cultures of the same sites on multiple occasions during a minimum 28-day hospitalization. They were given oral nonabsorbable antibiotics to suppress the organisms colonizing the alimentary canal and used techniques for preventing the acquisition of new organisms, such as the cooked-food diet, improved handwashing, and attention to water and ice supplies.

Specimens for culture were obtained by a microbiologist using moistened sterile cotton-tipped applicators. The samples were plated onto multiple media. Isolates of all morphologically distinct colonies were identified to species level. *Pseudomonas aeruginosa* was serotyped because of the known pathogenicity of this organism in granulocytopenic cancer patients (*3*). Antimicrobial susceptibility tests by the Kirby-Bauer method were made for each gram-negative bacillus on the initial cultures and repeated intermittently to check for the development of resistance patterns (*4*).

Since those studies were completed, we have continued to do surveillance cultures of anterior nares, gingiva, and rectal mucosa to evaluate for the presence of bacteria and fungi. These cultures are done at admission and weekly thereafter. Although the principle purpose is for research, we use the resultant data for patient care decisions on a daily basis.

At other centers, pharyngeal swabs and oral rinses have been used rather than gingival swab cultures and stool samples have been used rather than swabs of the rectal mucosa. Comparative data to suggest an advantage of one method over another are limited.

EPIDEMIOLOGY

Colonization

Infection is caused by organisms colonizing the patient at or near the site of infection. Multiple studies, especially those of patients with acute leukemia undergoing induction chemotherapy or receiving a bone marrow transplant, have indicated that the vast majority of infections are caused by organisms already colonizing the patient at or adjacent to the site ultimately infected.

Shifts in Microbial Flora

Illness and antimicrobial agents each create shifts of microbial flora. Studies by Johanson et al. (*5*) demonstrated that illness per se leads to shifts in the oral flora from the normal gram-positive aerobes and anaerobes toward gram-negative aerobic bacilli. The greater the degree of illness, e.g., myocardial infarction versus fracture, the greater the shift toward gram-negative bacilli. Follow-up investigations have shown that the etiology of pneumonia is closely related to the oral flora and that shifts toward more gram-negative bacilli binding to the oral epithelial cells will lead to gram-negative pneumonia. It has been possible to observe shifts of microbial flora of cancer

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Table 1. Organisms colonizing 135 newly diagnosed AML patients not taking antibiotics at admission[a]

Organism	Positive samples (%)			
	Nose	Gingiva	Axilla	Rectum
Pseudomonas aeruginosa	0	3	2	10
Escherichia coli	7	9	4	79
Klebsiella pneumoniae	3	9	11	22
Enterobacter spp.	14	10	11	15
Proteus mirabilis	10	3	9	12

[a]From Newman et al. (2).

Table 2. Organism acquisition among 97 AML patients receiving initial remission induction chemotherapy[a]

Organism	Positive samples			
	Nose	Gingiva	Axilla	Rectum
Pseudomonas aeruginosa	3%	7%	5%	11%
Escherichia coli	1%	5%	1%	38%
Klebsiella pneumoniae	0%	10%	1%	17%
Enterobacter spp.	3%	15%	1%	22%
Total No. of gram-negative rods acquired	18	82	19	206

[a]From Newman et al. (2). Patients were hospitalized for at least 28 days, and cultures were done twice a week.

patients in the oral cavity, on the skin, in the anterior nares, at the perianum, and on foreign bodies (e.g., Hickman catheters) by performing repetitive surveillance cultures. Bacterial and fungal surveillance cultures from the oral cavity of newly diagnosed leukemia patients have clearly demonstrated the shift from aerobic and anaerobic gram-positive cocci toward gram-negative aerobic bacilli as a consequence of illness and in the absence of antimicrobial therapy (table 1). Gingival cultures of 135 patients newly diagnosed and not treated with antibiotics, demonstrated that 3% were already colonized with *Pseudomonas aeruginosa*, 9% with *Escherichia coli*, and 9% with *Klebsiella pneumoniae*, these being the three most common causes of gram-negative bacteremia in granulocytopenic patients with acute leukemia (2). Furthermore, as remission induction chemotherapy continues, many patients will acquire gram-negative rods from the hospital environment (table 2). Again, focusing on the gingiva, serial surveillance cultures demonstrated that 7% acquired *P. aeruginosa*, 5% acquired *E. coli*, and 10% acquired *K. pneumoniae*. Overall, this group of patients became colonized by 82 acquired aerobic gram-negative bacilli.

The addition of antimicrobial therapy causes further shifts toward gram-negative rods resistant to commonly used antimicrobial agents and toward colonization with yeasts, particularly species of *Candida*. These changes have implications not only for oral infections but also for infections in the distal esophagus and in the lower respiratory tract, since the major source of organisms for esophagitis and pneumonitis in this patient population are those that colonize the oral cavity.

Variations in Virulence and Pathogenicity

Despite the extreme deficit in host defenses, principally granulocytopenia, in these patients, not all organisms are equally virulent or pathogenic. For example, nearly all patients colonized with *Pseudomonas aeruginosa* will develop infection, usually with bacteremia, if the granulocyte count is $<100/\mu L$ for more than a few days (3,4). Conversely, other species of *Pseudomonas*, *Proteus*, and *Citrobacter* are rarely associated with subsequent bacteremia, with *Escherichia coli* and *Klebsiella pneumoniae* being somewhat intermediate in pathogenicity (tables 3 and 4) (2,4,6).

As regards fungi, *Candida tropicalis* is more invasive than *C. albicans*, and *Aspergillus flavus* and *A. fumigatus* are more invasive in neutropenic patients than is *A. niger*. Sandford et al. (7) demonstrated that three of 60 patients colonized with *C. albicans* developed systemic infection, whereas 15 of 25 patients colonized with *C. tropicalis* progressed to fungemia. These investigators have shown that local mucosal conditions related to colonization, administration of chemotherapy, and antibiotics are critical to invasion but that when these are held constant, *C. tropicalis* is still markedly more virulent than *C. albicans* (8).

The number of sites colonized seems to correlate with the likelihood of infection. *Torulopsis glabrata* serves as a useful example while emphasizing the value of surveillance cultures in understanding the epidemiology of infection by this yeast (table 5). Among 157 colonized patients over a 48-month period,

Table 3. Pathogenicity of isolates from 48 AML patients undergoing remission induction chemotherapy[a]

Organism	At admission		During hospitalization	
	No. of patients colonized	No. (%) of colonized patients infected	No. of patients colonized	No. (%) of colonized patients infected
Pseudomonas aeruginosa	9	8 (89)	22	15 (68)
Escherichia coli	34	7 (21)	8	0
Klebsiella pneumoniae	25	4 (16)	17	5 (29)
Staphylococcus aureus	14	5 (36)	12	5 (42)
Candida albicans	21	8 (38)	18	3 (17)
Pseudomonas (non-*aeruginosa*)	4	0	25	0
Enterobacter cloacae	11	0	22	1
Group D streptococci	30	2	14	2

[a]From Schimpff et al. (4).

Table 4. Colonization and subsequent infection among 33 patients with acute leukemia[a]

Organism	No. of patients			
	At admission		During hospitalization	
	Colonized	Infected	Colonized	Infected
Pseudomonas spp.	6	5	8	5
Klebsiella spp.	19	2	21	5
Escherichia spp.	57	1	2	2
Staphylococcus aureus	0	0	3	2

[a]From Fainstein et al. (*6*).

Table 5. Effect of colonization with *T. glabrata* on infection frequency[a]

No. of sites colonized	No. of patients		
	Colonized and infected	Colonized but not infected	Infected/colonized (% infected)
≤2	7	116	7/123 (6)
>2	10	24	10/34 (29)[b]
All	17	140	17/157 (11)

[a]From Aisner et al. (*9*). Prior surveillance cultures were obtained for 19 patients, two of whom were found not to be colonized.
[b]$P < .0005$ versus ≤2 sites colonized.

seven (6%) of 123 colonized at ≤2 sites developed infection, whereas 10 (29%) of 34 colonized at more than two sites became infected (*9*).

PREVENTION OF INFECTION

Surveillance cultures have been useful in evaluating the effectiveness of a variety of preventive measures initiated to reduce acquisition of new organisms and suppress colonizing organisms.

Surveillance cultures documented that intense and thorough approaches to total reverse isolation, as found in life islands and laminar air flow rooms, do indeed reduce the acquisition of new organisms. Unfortunately, only limited data are available about specific individual aspects such as handwashing, low-microbe-content diet, and use of antiseptics by housekeepers.

Surveillance cultures have also been useful in determining whether antimicrobial agents have been successful in suppressing organisms. There have been studies assessing orally nonabsorbable antibiotics, orally absorbable antibiotics, and, to a lesser degree, the effects of systemically administered antimicrobial agents. Not surprisingly, most data relate to colonization with bacteria, but there is an increasingly large data base related to yeasts and some filamentous fungi. In addition, given the high incidence of herpes simplex virus infections in bone marrow transplant recipients, surveillance cultures have been useful in assessing the efficacy of antiviral prophylaxis (e.g., with acyclovir).

In an evaluation of 62 acute myelocytic leukemia (AML) patients receiving remission induction chemotherapy and selective microbial suppression, the presence or absence of colonization correlated with subsequent infection when the granulocyte count was <100/μL (table 6) (*10*). Similarly, an investigation of 50 patients (table 7) with acute leukemia, who were receiving remission induction chemotherapy while isolated and also receiving antimicrobial flora modulation, demonstrated the conjoined importance of both granulocytopenia and the presence or absence of gram-negative bacilli in oral washing samples (*11*). Overall, 46% of patients with effective flora modulation (i.e., no gram-negative rods detected) developed ororespiratory infection (i.e., stomatitis, tonsillitis, pharyngitis, bronchitis, or pneumonitis) compared with 75% of patients who had gram-negative rods isolated during the baseline period and 86% of patients who acquired them during hospitalization.

The combination of gram-negative organisms in oral washings plus profound (<100/μL) granulocytopenia leads to a striking degree of time with ororespiratory infections (fig. 1), with acquisition of these organisms being more relevant than the presence of these organisms at admission (*11*).

In a placebo-controlled trial of selective antimicrobial agent modulation of patient flora, only one major gram-negative rod infection occurred among the 16 patients receiving selective antimicrobial modulation. Seven serious gram-negative infections occurred among the 17 placebo-treated patients. These data correlated well with the bacteriologic monitoring from surveillance cultures of stool samples (fig. 2) (*12*).

Herpes simplex virus is a major cause of oral infection in bone marrow transplantation patients. Meyers et al. (*13*) found that 62 of 76 (82%) seropositive patients but only one of 65 seronegative patients developed overt herpes simplex virus

Table 6. Selective microbial suppression[a]

Organism	Colonized (No. of patients)	No. (%) of patients infected	% Probability of infection[b]
Staphylococcus aureus	Yes (23)	11 (48)	27–69
	No (39)	2 (5)	0.6–17
Pseudomonas aeruginosa	Yes (8)	5 (62)	25–91
	No (54)	1 (2)	0–10
Enterobacteriaceae	Yes (19)	8 (42)	20–66
	No (43)	1 (2)	0–12

[a]From Guiot et al. (*10*). Data are for 62 AML patients undergoing remission induction who had granulocyte counts <100/μL.
[b]95% confidence interval.

Table 7. Ororespiratory infections among 50 acute leukemia patients receiving antimicrobial flora modulation therapy[a]

Gram-negative bacilli in oropharynx	No. of patients	No. (%) infected
None present	24	11 (46)
Present at admission	12	9 (75)[b]
Acquired during hospitalization	14	12 (86)

[a] From Kurrle et al. (*11*).
[b] $P < .05$ versus patients with no gram-negative bacilli present in oropharynx.

infection during the 4 months immediately following transplantation. Saral et al. (*14*) demonstrated that acyclovir could largely eliminate these reactivations of herpes simplex virus. Seven of 10 seropositive patients receiving placebo developed herpes simplex virus infection following marrow transplant, whereas none of 10 became infected while receiving acyclovir.

Surveillance studies indicate that *Staphylococcus aureus* causes infection principally among patients with nasal colonization. Elimination of nasal carriage might reduce the frequency of infection. Rifampin appears to be effective in this regard, although resistance may develop. Sande and Mandell (*15*) obtained anterior nares cultures every 3 months for 1 year from patients at a tuberculosis hospital. Carriage rates were 1.7% for the 227 patients whose antituberculous regimen included rifampin, 7.8% among 190 patients not receiving rifampin, and 14.2% among 98 employees. The four strains isolated from rifampin-treated patients were resistant; all 16 strains from the other patients and 15 of 16 from employees were not resistant to rifampin (*15*).

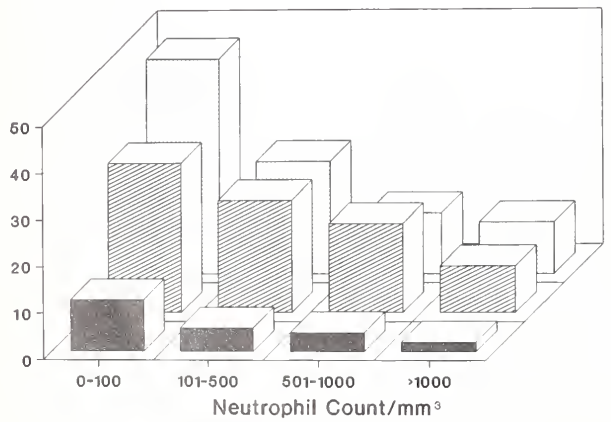

Figure 1. Correlation between ororespiratory infections, oral microbial flora, and granulocytopenia. Symbols: solid boxes, group I (no gram-negative rods in oral flora at baseline); hatched boxes, group II (gram-negative rods in oral flora at baseline); stippled boxes, group III (acquisition of gram-negative rods in oral flora). The left-hand scale represents % of time with ororespiratory infection. [Reprinted from Kurrle et al. (*11*) with permission. Copyright 1981, University of Chicago Press.]

THERAPY OF INFECTION

Colonization Patterns

The design of an empiric antimicrobial regimen depends on a clinical epidemiological base of information on the types of infections occurring in a given population within a specific institution and even within a specific area of that institution. Knowledge of the most common infecting organisms, sites of infection, and patterns relative to superinfection is highly useful in designing empiric regimens. Surveillance cultures, although not essential, can be of added assistance in indicating what potential pathogens are currently tending to colonize patients within a unit. Moreover, with regard to a specific patient, surveillance culture data may give clues to the most likely pathogen once fever develops. For example, a patient colonized with *Pseudomonas aeruginosa* who is granulocytopenic and develops new fever should certainly be treated with presumptive therapy effective for *Pseudomonas* bacteremia (*4,6*).

Resistant Organisms

There are two important issues in assessment for resistant organisms. First, patients who have been receiving oral prophylactic antimicrobial agents may have become colonized with an organism resistant to one or more of the prophylactic agents. Gentamicin, vancomycin, and nystatin and similar nonabsorbable drugs have been used in attempts to suppress the alimentary canal microbial flora as completely as possible. Surveillance cultures have shown that when compliance is excellent, oral cultures nearly always remain positive. Cultures of the stool, where the concentration of antibiotic is high, may be negative, but cultures based on swabbing the rectal mucosa will usually demonstrate the organisms present, albeit in low concentration, before antibiotic therapy was begun. If antibiotic therapy is discontinued before the granulocyte count returns to normal, the flora that regrows first and fastest consists principally of aerobic gram-negative bacilli, which in turn often proceed to invade the mucosa and cause bacteremia (*16*).

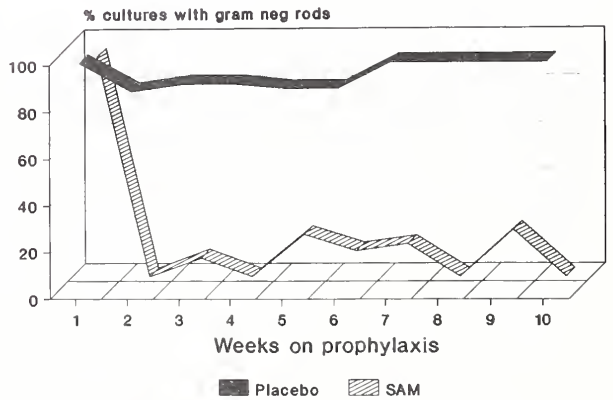

Figure 2. Anaerobic and facultative anaerobic gram-negative rods cultured from stool samples of ANLL patients who received a selective antimicrobial modulation (SAM) regimen or placebo. [Reprinted from Guiot et al. (*12*) with permission. Copyright 1983, University of Chicago Press.]

Selective microbial suppression with agents such as trimethoprim-sulfamethoxazole (TMP-SMX) or a quinolone (norfloxacin, ciprofloxacin) does not suppress the anaerobic flora and, hence, presumably preserves colonization resistance. However, many patients receiving TMP-SMX have been found to become colonized with multiple-resistant gram-negative bacilli (*17,18*). When this occurs, it may be wise to add another agent to suppress the resistant strain, as it is usually also resistant to many of the agents commonly used for systemic empiric therapy.

Second, surveillance cultures may indicate the presence of one or more organisms resistant to the current standard empiric regimen. In the first case, prophylaxis may need to be altered as part of the attempt to prevent infection from occurring. In the second case, the choice of empiric regimen can be adjusted at the onset of fever by recognizing the presence of a specific resistance pattern.

Ticarcillin plus gentamicin was the standard empiric regimen at Johns Hopkins Hospital a few years ago. Eighty-six bone marrow transplantation patients had surveillance cultures of stool samples performed to determine the presence or absence of gram-negative rods resistant to ticarcillin, gentamicin, or both (table 8). These patients received no antimicrobial prophylaxis but were housed in rooms with HEPA air filtration. Forty-eight resistant gram-negative rods were isolated one or more times from 35 of the 86 patients. Twelve of the 48 resistant strains (25%) subsequently caused infection. Persistent colonization was more likely to lead to infection (seven of 13) than was transient (i.e., one positive culture) detection (five of 35). Only three of 54 (6%) patients with no documentation of resistant strains became infected with a resistant organism.

To summarize, resistant organisms were frequent; one third were present before any antibiotic therapy had been instituted; most were acquired in the hospital. The positive predictive value of the surveillance cultures was low (25%–54%), but the negative predictive value was high (91%–94%) (*19*).

Table 8. Association of colonization and infection due to antibiotic-resistant bacteria in 86 consecutive allogeneic BMT patients[a]

Colonization	No. of patients	
	Infected	Noninfected
Patients colonized[c]	12	36
Once	5	30
Persistently[d]	7	6
Patients not colonized	3	51

[a] From Wingard et al. (*19*).

[b] Patients colonized by more than one antibiotic-resistant organism were counted once for each organism.

[c] Patients colonized at least once were more likely to become infected than those not colonized ($P = .006$).

[d] Patients persistently colonized were more likely to become infected than those not colonized only once ($P = .01$).

Nonresponding Patients

Many patients who develop fever during granulocytopenia and are placed on empiric antibiotic therapy will still be febrile or demonstrate other evidence of nonresponse a few days later, or there may be concern that a secondary or superinfection has occurred. Surveillance cultures taken at the time of the diagnostic evaluation when fever first began may be helpful at this juncture. For example, the presence of a gram-negative rod resistant to gentamicin might lead to a switch to amikacin. The isolation of methicillin-resistant *Staphylococcus aureus* or *Staphylococcus epidermidis* in high numbers from multiple sites might lead to the addition of vancomycin to the regimen. The presence of *Candida albicans*, *Candida tropicalis*, or *Torulopsis glabrata* at multiple sites, especially in the patient with some degree of dysphagia or some vague abdominal discomfort in the setting of minimal or no response to the current antimicrobial regimen, might lead to the institution of amphotericin B therapy. The finding of *Clostridium difficile* along with diarrhea and abdominal discomfort even in the absence of documented toxin production might be sufficient for instituting oral vancomycin therapy. The finding of herpes simplex virus in a patient with oral lesions could be cause for the addition of acyclovir. The isolation of *Aspergillus flavus* from nose cultures in a setting of sinusitis might likewise lead to the use of amphotericin B. This latter case will be used as a final example. Over a 3-year period, 125 patients with AML were followed with routine surveillance cultures of the anterior nares. Eighteen of these patients developed invasive aspergillosis (table 9). There was a high correlation between nares cultures positive for *A. flavus* or *A. fumigatus* and subsequent invasive infection (*20*).

Table 9. Nasal surveillance cultures and aspergillosis among 125 AML patients[a]

Nose culture result	No. of patients	No. (%) developing aspergillosis
Positive[b]	11	10 (91)
Negative	114	8 (7)

[a] From Aisner et al. (*20*).

[b] *Aspergillus flavus* or *A. fumigatus* isolated on one or more occasions.

It needs to be reemphasized that the use of surveillance cultures as outlined above is not appropriate for all cancer patients and not appropriate even for all patients with acute leukemia. The major use for surveillance over the years has been in understanding the epidemiology of infection in these patients for research purposes. This clearly need not be repeated on each and every patient in multiple institutions. On the other hand, for the patient with profound (<100 granulocytes/μL) or persistent (≥10–14 days) granulocytopenia, there is a very high likelihood of infection, and in this subgroup of patients, surveillance cultures have been found to be useful for monitoring prevention measures and for assisting in the choice or modification of therapeutic measures. Surveillance cultures should be undertaken only when the physician is clear about the specific purpose for their use and when it is clear how the information derived will be used.

It is worth emphasizing that most hospital microbiology laboratories are not accustomed to performing surveillance cultures and, hence, will report back information of little or no value. If surveillance cultures are to be used, they should be done in consultation and agreement with the director of the microbiology laboratory so that samples can be plated onto

multiple special media, isolates of all morphologically distinct colonies can be identified to species level, and antimicrobial susceptibility tests can be done for each gram-negative bacillus, *Staphylococcus aureus,* and *Staphylococcus epidermidis*. We have found that the most useful sites for surveillance cultures are the anterior nares, gingiva, and perianum.

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Role of Surveillance Cultures in Prevention and Treatment of Fungal Infections

Thomas J. Walsh

Fungal surveillance cultures have been studied as potential predictors of invasive or disseminated mycoses. Several studies have demonstrated that the presence of *Candida tropicalis* in mucosal surveillance cultures has a high predictive value for invasive fungal infection due to this pathogen in granulocytopenic patients. By comparison, surveillance cultures for *Candida albicans* have a poor positive predictive value for invasive fungal infection. The value of routine surveillance cultures of the nares for *Aspergillus* spp. has not been consistently confirmed. The use of surveillance cultures for less common fungal pathogens, such as *Trichosporon beigelii*, also remains unclear. Fungal surveillance cultures of the inanimate hospital environment have proven useful in identifying the source of conidia in well-defined clusters or outbreaks of nosocomial aspergillosis and other mycoses. As investigational tools, fungal surveillance cultures also may be useful for studying the effects of new antifungal agents on mucosal flora. Fungal surveillance cultures, especially for *C. tropicalis* and possibly *Aspergillus* spp. in high-risk populations, may be useful when a pathogen-directed approach to antifungal therapy is used. However, the time required, diagnostic limitations, and expense of routine mucosal fungal surveillance cultures must be balanced against the effect of this information on therapeutic decisions. Empirical antifungal therapy and early diagnostic approaches for high-risk patients may obviate the need for routine fungal surveillance cultures while decreasing the frequency of invasive mycoses. [NCI Monogr 9:43–45, 1990]

Invasive fungal infections are common complications reported with increasing frequency among patients receiving treatment for neoplastic diseases. These invasive mycoses are the cause of substantial morbidity and mortality in patients receiving aggressive cytotoxic chemotherapy. The problem of invasive mycoses is further complicated by the appearance of new fungal pathogens and increasing reports of emergence of resistance to established antifungal compounds.

Fungal infections of the oral cavity, especially those due to *Candida* spp., are especially common in the granulocytopenic patient population and are the cause of significant discomfort, a deterrent to adequate nutrition, and often the harbinger to systemic infection. Fungal infections of the oral cavity may also indicate involvement of the esophagus and gastrointestinal tract. The infected alimentary tract may also serve as the portal of entry for systemic infection involving sites such as the liver, spleen, kidneys, heart, eyes, and brain.

The role of surveillance cultures in the detection of fungi in granulocytopenic patients has been controversial. Potential sites of surveillance include the oral cavity (gingiva, buccal mucosa, and oropharynx), nares, skin, anorectal region, and blood.

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For the purposes of this discussion, a fungal surveillance culture is defined as a culture of a mucosal surface sample from patients not considered to have an active fungal infection when the presence of fungi may permit early diagnostic or therapeutic intervention.

COMMON FUNGAL INFECTIONS

Most of the mycoses complicating antineoplastic chemotherapy are nosocomial fungal infections. The nosocomial mycoses have been recently classified by Walsh and Pizzo (*1*) as being either type I (hospital acquired) or type II (hospital associated). For example, most cases of nosocomial aspergillosis have been type I. Most cases of nosocomial candidiasis are type II, arise from endogenous flora, and are hospital associated.

Numerous studies have been conducted on the etiology, complications, and management of oropharyngeal candidiasis (*2–8*). One such study, by Meunier et al. (*8*), presents the typical spectrum of *Candida* species causing oropharyngeal candidiasis. The predominant organism is *Candida albicans*, followed by *Candida tropicalis* and then by other species, including *Torulopsis glabrata* and *Candida parapsilosis*. Mixed infections due to these and other species are not uncommon.

One of the early and important studies evaluating the role of surveillance cultures for *Candida* spp. and other fungi as potential predictors of systemic fungal infections was that of Sanford et al. in 1980 (*9*). Fungal surveillance cultures of urine, stool, and respiratory specimens were reviewed from 37 bone marrow transplant recipients and 52 patients with hematological malignancies. Among these patients, 67% were colonized by *C. albicans*, 28% by *C. tropicalis*, and none by *Aspergillus* spp. There were 21 systemic fungal infections; three were due to *C. albicans*, 16 were due to *C. tropicalis*, and two were due to *Aspergillus* spp.

PREDICTIVE VALUE OF SURVEILLANCE CULTURES

The positive predictive value of cultures for patients colonized at one or more sites by *C. tropicalis* was 60%, but for *C. albicans* it was only 2%. By comparison, the negative predictive value of one or more surveillance cultures negative for *C. tropicalis* was 98% and for *C. albicans* was 100%. Thus, the positive predictive value for *C. tropicalis* was good but that for *C. albicans* was not. Pfaller et al. (*10*) also evaluated the positive and negative predictive value of weekly or twice-weekly surveillance cultures for patients with hematologic malignancies or receiving bone marrow transplantation. Positive surveillance cultures in this study also correlated with invasive disease due to *C. tropicalis*. Positive surveillance

cultures for *C. albicans* did not correlate with invasive candidiasis; however, negative surveillance cultures for *C. albicans* and *C. tropicalis* had a high negative predictive value of 95%–99%.

Caution should be exerted, however, in excluding an invasive fungal infection in a persistently febrile granulocytopenic patient whose mucosal surveillance cultures are negative. The utility of mucosal surveillance cultures for *Candida* spp. assumes to some extent that the gastrointestinal tract is the portal of entry for deep infection. However, central silastic venous catheters may also be a portal of entry for disseminated candidiasis. Lecciones et al. (*11*) found that 50% (26 of 52) of all episodes of venous catheter-associated fungemia showed positive blood cultures exclusively from the venous catheter. Karabanis et al. (*12*) performed a multivariate analysis of risk factors for candidemia. Among 30 cancer patients with candidemia in comparison to 58 matched control patients, the following variables in a multivariate logistic model were found to be significant risk factors for candidemia: positive peripheral cultures for *Candida* spp., central venous catheterization, and neutropenia. Negative mucosal surveillance cultures do not necessarily exclude a contaminated venous catheter as the portal of entry for *Candida* spp. Blood cultures from a febrile immunocompromised patient with a primary catheter infection that are positive for *Candida* spp. may be the first indicator of disseminated candidiasis.

A study by Kramer et al. (*13*) in 1982 evaluated serial microbiological surveillance cultures for 271 patients with 652 episodes of fever and granulocytopenia. Due to the poor predictive value of surveillance cultures, this study could not justify the cost of routine fungal surveillance cultures for granulocytopenic patients.

LESS COMMON PATHOGENS

Other fungi have been identified as uncommon but emerging pathogens. *Trichosporon* spp. are one such group of yeastlike fungal pathogens. A study conducted by Walsh et al. (*14*) found that among 15 patients colonized or infected by *Trichosporon* spp., four of five patients (80%) with disseminated infection had negative surveillance cultures. Conversely, five colonized granulocytopenic patients did not develop active infection. Moreover, multiple cultures of the environment did not reveal *Trichosporon* spp. However, Haupt et al. (*15*) found that positive urine cultures preceded the development of trichosporonemia in granulocytopenic patients. Differences in surveillance techniques, patient populations, protocols of antineoplastic therapy, and use of empirical amphotericin B may account for the differences between these studies.

Several studies, however, have demonstrated the value of fungal cultures of the respiratory tract for early detection of pulmonary aspergillosis (*16–18*). Aisner et al. (*16*) in 1979 demonstrated that positive nasal surveillance cultures were predictive of the development of pulmonary aspergillosis during an ongoing outbreak of nosocomial aspergillosis in patients with hematological malignancies. Ten of 11 patients with positive nasal surveillance cultures acquired sinus or pulmonary aspergillosis; in comparison, eight of 114 patients with negative nasal surveillance cultures acquired aspergillosis. The predictive value of such surveillance has not been consistently corroborated by other institutions with different patient populations, environmental microbiology, and hospital epidemiology. Nevertheless, two studies, by Treger et al. (*17*) and by Yu et al. (*18*), have demonstrated the predictive value of lower respiratory tract cultures for high-risk granulocytopenic patients. However, these cultures are diagnostic cultures for high-risk patients, not surveillance cultures.

COMPARISON WITH BACTERIAL SURVEILLANCE CULTURES

Several comparisons may be drawn between fungal surveillance cultures and bacterial surveillance cultures. Both fungal and bacterial surveillance cultures have been studied for granulocytopenic patients in order to characterize the epidemiology of shifting mucosal flora and to monitor for the most likely invasive pathogens (*19*). Fungal and bacterial surveillance cultures have also been studied in order to monitor the inanimate environment for environmental sources of infectious pathogens. Environmental fungal surveillance cultures have been best used in the investigation of defined outbreaks and clusters of nosocomial aspergillosis and are discussed in detail elsewhere (*20*). Bacterial surveillance cultures have been studied for detecting the emergence of resistant gram-negative bacilli in granulocytopenic patients. However, the detection of polyene-resistant fungi in granulocytopenic patients has limited therapeutic options. Nevertheless, several new potent antifungal triazoles, liposomal formulations of amphotericin B, echinocandin analogues, and use of higher doses of amphotericin B with or without concomitant flucytosine offer potential therapeutic alternatives for polyene-resistant fungi (*21*). The detection and management of polyene-resistant fungi remain investigational at this time. Fungal surveillance cultures will continue to provide information as research tools in studying the effects of investigational antifungal agents on the fungal flora of mucosal surfaces.

EMPIRICAL ANTIFUNGAL THERAPY

As fungal surveillance cultures, blood cultures, and other diagnostic modalities were found to have limited value for early recognition of the common invasive mycoses and since delays in diagnosis were associated with high mortality, Pizzo et al. (*22*) studied the role of empirical antifungal therapy in cancer patients with prolonged fever and granulocytopenia. Among 271 patients with 652 episodes of fever and granulocytopenia, those with persistent fever and granulocytopenia were randomized to one of three groups: discontinuation of antibiotics; continuation of antibiotics; and continuation of antibiotics with addition of amphotericin B. Among those who stopped taking antibiotics, six developed bacterial sepsis. Among those continuing to receive antibiotics, five of 16 developed fungal infections, compared to one of 18 who continued to receive antibiotics and who also received amphotericin B. Empirical antifungal therapy therefore reduced the development of invasive fungal infections in high-risk patients. Moreover, surveillance culture data were not required.

A more recent study of empirical amphotericin B therapy conducted by the European Organization for Research in the Treatment of Cancer corroborated its value in decreasing invasive fungal infections in persistently febrile granulocytopenic patients (*23*). This study further identified certain patient populations that may benefit further from empirical amphoteri-

cin B. These include patients with profound granulocytopenia (<100/μL) and those not receiving prophylactic antifungal regimens. Again, surveillance culture data would not be required in the decision to administer antifungal therapy when empirical amphotericin B is used.

SUMMARY

The utility of surveillance cultures may be influenced by an institutions's therapeutic approach to invasive fungal infections. A pathogen-directed approach, which may otherwise delay early treatment, may find the data gleaned by surveillance cultures to be useful. An empirical approach to antifungal therapy in high-risk granulocytopenic patients permits early treatment of invasive mycoses without dependence on surveillance cultures.

Fungal surveillance cultures, especially for *C. tropicalis* and possibly *Aspergillus* spp. in high-risk populations, may be useful when a pathogen-directed approach to antifungal therapy is used. However, the time required, diagnostic limitations, and expense of fungal surveillance cultures must be balanced against the effect of this information on therapeutic decisions. Empirical antifungal therapy and early diagnostic approaches for high-risk patients may obviate the need for routine fungal surveillance cultures.

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III. Pretreatment Strategies

Prechemotherapy Dental Treatment To Prevent Bacteremia

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Infection is the most common cause of morbidity and death in patients receiving chemotherapy for treatment of acute leukemia. Studies performed during the past decade suggest that over 30% of these infections originate from oral sources, particularly periodontal pockets and pericoronal flaps. Studies of large numbers of patients receiving a variety of myelosuppressive chemotherapy protocols are necessary to determine the risk-benefit ratio of dental treatment prior to chemotherapy. [NCI Monogr 9:49–50, 1990]

The major oral complications of cancer chemotherapy are infection, mucositis, and bleeding. The most clinically significant problem is infection, which has been shown in several studies to be the most common cause of morbidity and death in patients receiving myelosuppressive and immunosuppressive doses of chemotherapy. The group of cancer patients most widely studied for oral infections is patients receiving chemotherapy to treat acute leukemia. Prior to this decade, it was recommended that patients with newly diagnosed leukemia not receive dental treatment until the leukemia was in remission. It was considered far too risky to provide dental treatment for leukemic patients because they have thrombocytopenia, neutropenia, and leukocyte dysfunction, predisposing them to bleeding and infection. The results of recent studies are altering that opinion as well as current standards of care, since these results suggest that untreated dental disease creates a significant risk of serious generalized infection during chemotherapy and that eliminating sources of dental infection reduces that risk.

In 1980, Peterson et al. (*1*) presented a study of 19 leukemia patients with moderate to severe periodontal disease. Patients were randomly assigned to receive either limited or intensive oral hygiene prior to and during chemotherapy. Seven patients receiving limited oral hygiene developed acute periodontal infections during chemotherapy. None of the patients in the intensive oral hygiene group developed infections. The relationship of these local periodontal infections to generalized infection was not part of this study. Peterson and Overholser (*2*) also carried out a retrospective study of 38 acute leukemia patients. Twelve of the 38 patients studied developed a fever associated with an oral infection during chemotherapy. The most frequent source of infection was oral, which accounted for 32% of all infections associated with fever. The most common cause of oral infection was periodontal disease.

In 1982, my group at the University of Pennsylvania (*3*) published a prospective study of oral infection as a cause of septicemia in 33 patients with acute leukemia. During the initial stages of the study, the following protocol was followed. All patients admitted to the Oncology Unit of the Hospital of the University of Pennsylvania with acute nonlymphocytic leukemia who developed fevers of 101 °F (ca. 38 °C) or greater for 8 consecutive hours were included in the study. General information obtained for each febrile leukemic patient included daily records of chemotherapeutic drugs and antibiotics taken and total and differential white blood cell counts. A daily history and complete physical examination were done to detect signs and symptoms of infection. Particularly emphasized were the lungs, urinary tract, skin, and rectum, areas associated with infection by previous investigators. During each febrile episode, blood cultures for aerobic and anaerobic organisms were done along with routine cultures of stool, sputum, urine, and throat samples. Each febrile patient was questioned and examined daily by a dental investigator for signs and symptoms of oral disease. A panoramic X-ray was obtained for diagnosis of periapical, periodontal, or pulpal infection. Questionable teeth were pulp tested. The following oral samples were obtained: a general swab of the oral mucosa done by running a sterile Dacron swab across the buccal mucosa, floor of the mouth, and tongue; samples of the gingival sulcus, obtained by gently running a thin periodontal curette into the sulcus around the buccal surfaces of each of the remaining teeth and placing it on a sterile Dacron swab; and additional samples from oral ulcers or sites of clinical infection. These studies were repeated each day that the patient was febrile.

Cultures were analyzed for the presence of organisms previously associated with septicemia in myelosuppressed and immunosuppressed patients, particularly *Pseudomonas* spp., enterobacteria such as *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp., and *Candida*, *Aspergillus*, and Phycomycetes (Zygomycetes) fungi.

At the end of each febrile episode, the clinical and laboratory data were reviewed by the investigating dentist, hematologist, and microbiologist. The fevers were divided into four categories: fever of unknown origin, septicemia only, local infection only, and local infection with septicemia. Patients in the last category were subdivided into five categories depending on the site of origin of their septicemia. These five categories were oral site, likely oral site, likely extraoral site, extraoral site, and site unknown. The criteria used to categorize the septicemia originating from an oral source were: the patient had localized oral signs and symptoms; other signs and symptoms were not present; the same organism was cultured from the blood and in moderate to heavy amounts from the oral infection; and the organism was not cultured from other body sites.

A preliminary data analysis was carried out after the study of the first nine leukemia patients. This group of nine consisted of six men and three women ranging in age from 24 to 66 years. During their hospitalization, these nine patients experienced 15 febrile episodes. Seven of the 15 fevers were associated with septicemia. The etiologies of the 15 fevers were as follows: three cases of pneumonia, one urinary tract infection, one drug

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reaction, four fevers of unknown origin, and six oral infections. Four of the six oral infections were associated with the onset of septicemia, with the same bacteria isolated from the oral infection as from the blood.

In summary, nine patients experienced 15 fevers. Six of the 15 febrile episodes appeared to be related to an oral infection, and in four of the six cases, the oral infection was considered the most likely cause of septicemia. The predominant bacteria isolated in each of the four cases of oral infection with septicemia were *Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus epidermidis*. These initial data suggested a significant incidence of oral sources of septicemia, and it was considered unethical to leave obvious sources of bacteremia present. The protocol was therefore changed as follows. Each leukemia patient would be screened by a dental investigator before chemotherapy was begun and examined clinically and radiographically for the presence of advanced periodontal disease, chronic abscesses, nonvital teeth, and pericoronal flaps. Obvious potential sources of infection would be removed whenever possible prior to chemotherapy. Prechemotherapy cultures of the oral mucosa and gingival sulcus would also be obtained. Febrile patients would be studied in the manner described previously. In addition, whenever the same species of organism was isolated from the blood and the mouth, the bacteria were biotyped. An antibiogram was also performed to demonstrate susceptibility and resistance patterns. If the results of the API 20E (Analytab Products) and antibiogram were identical, organisms from the blood and mouth were likely to be the same.

Twenty-four additional patients with acute leukemia were studied in this manner. The 24 patients consisted of 13 men and 11 women whose ages ranged from 20 to 72 years. Dental treatment was provided to nine of these 24 patients prior to chemotherapy: periodontal therapy in only three cases, extractions in only three cases, and periodontal therapy plus extractions in another three cases. The 24 patients had a total of 55 fevers. The cause of the fever could be identified in 30 of the 55 cases. The most commonly identified local infection was pneumonia. Six of the fevers were caused by septicemia, which was confirmed by at least two positive blood cultures.

Klebsiella species were the cause of septicemia in four of the six cases. There were no cases of anaerobic septicemia or fungemia. In case 1, a *Klebsiella* sp. was isolated from the blood, the mouth, and the gastrointestinal tract. Since the patient had gastrointestinal symptoms, the gastrointestinal tract was considered the most likely source of the bacteremia. Case 2 was a staphylococcal septicemia most likely caused by an indwelling Hickman catheter. Patients 3 through 5 had moderate to moderately severe periodontal disease. The same organism (*Enterobacter cloacae, Klebsiella pneumoniae,* and *Klebsiella oxytoca)* was isolated from the gingival sulcus and the blood in each case. Biotyping and antibiotic susceptibility patterns gave identical results. The organism was not isolated from other routinely cultured body sites, and there were no other localizing signs or symptoms. In these three cases, the most likely source of septicemia was periodontal disease. In this study, there were a total of 13 cases of septicemia. In seven of the 13 cases (54%), oral and dental disease was the most likely source of infection.

During the past year, Bergman (*4*) carried out a similar study on a group of 46 patients receiving chemotherapy for hematologic malignancy. Febrile patients were studied with serial blood cultures and cultures of the gingival margin and oral sites of infection. Nineteen cases of septicemia developed in 46 patients. The most likely cause of septicemia in 32% (six of 19) was oral. The evidence indicates that oral and dental disease is an important source of septicemia during myelosuppressive chemotherapy.

In the future, prospective studies with a larger number of patients should be performed to further define the risk-benefit ratio of dental procedures prior to myelosuppressive chemotherapy. Particular attention should be paid to studies that help determine the extent of periodontal and pericoronal disease likely to cause serious complications during chemotherapy, as well as potential complications related to the dental treatment itself.

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Oral Antimicrobial Agents—Chlorhexidine

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Chlorhexidine's structural characteristics give it potent antimicrobial activity, effectiveness at low concentrations, substantivity that prolongs its therapeutic effect in the oral environment, minimal resorption from the gastrointestinal tract, and the ability to reduce plaque. The use of this agent for oral stomatitis in neoplasia patients has recently been studied. Treatment-associated oral soft tissue inflammation and ulceration were significantly reduced by chlorhexidine in patients undergoing intensive chemotherapy. Reductions in total streptococci and yeast counts were also observed. When used in conjunction with systemic antifungal agents, such as nystatin or clotrimazole, a significantly decreased incidence of clinical oral candidiasis and *Candida* septicemia was observed. In contrast, in two studies in which high-dose head and neck radiation therapy was applied, there was no reduction in stomatitis. Oral gram-negative bacilli have been shown to increase in high-dose chemotherapy patients who are taking chlorhexidine during the treatment period (3 wk to 2 mo). However, no increase in systemic gram-negative infections or other adverse negative medical consequences were observed. This agent appears to be of therapeutic benefit in reduction of dental plaque, gingivitis, and stomatitis in the high-risk chemotherapy population when used in conjunction with other topical and systemic antimicrobial agents as prophylaxis. Although no toxic or serious adverse effects of chlorhexidine rinse have been observed in the short-term studies to date, the effects of longer-term chlorhexidine administration should be evaluated. [NCI Monogr 9:51–55, 1990]

Treatment of malignant conditions and hematologic neoplasias with cytotoxic chemotherapy and radiation therapy is becoming increasingly more effective but is associated with significant side effects, including toxic effects to the nonhematopoietic tissues. Among these clinically important side effects are disruptions in the function and integrity of the mouth. The consequences of this include severe oral mucositis and gingivitis, oral candidiasis, xerostomia, cellulitis, and viral mucosal eruptions (*1–7*). Chemotherapeutic drugs and radiation, through inhibition of cell growth and maturation, disrupt the mucosal barrier of the upper aerodigestive tract, creating a portal of entry for the normal flora. The concurrent administration of oral broad-spectrum antibiotics causes shifts in the normal oral microflora that often permit fungal overgrowth. These combined effects predispose patients to systemic infections by organisms of oral origin. As an example, the high incidence and clinical consequences of candidiasis in immunosuppressed patients with cancer are well known. These treatment-associated oral complications may also produce severe local discomfort and pain, poor nutrition, delays in administration or dose limitations in antineoplastic treatments, increased hospital stays and costs, and, in some patients, life-threatening septicemia.

Mucositis and infections of the mouth have remained major sources of morbidity despite the usual oral care provided for cancer patients. Treatments studied have included frequent mouth cleaning and rinsing with buffered saline and fluoride solutions and administration of topical and systemic antimicrobial agents (*1,2,4–8*).

The recognition that compounds such as chlorhexidine have both broad-spectrum topical antimicrobial activity and properties that result in sustained binding to oral surfaces has provided a new approach to prophylaxis against gingival disease and other oral infections. If oral stomatitis in patients receiving chemoradiotherapy results largely from superinfection of a reversibly damaged mucosal barrier by oral flora, then appropriately timed use of an effective topical agent such as chlorhexidine might provide an improved method for prophylaxis of oral complications.

In a recent review, Kornman (*9*) classified topical compounds that inhibit or kill large numbers of oral bacteria by their substantivity in vivo as either first- or second-generation agents.

Briefly, first-generation agents are clearly antibacterial in vitro but have minimal substantivity, defined as the ability to be retained in the oral cavity and released slowly with continuous potency. These agents are limited in their ability to prevent or resolve signs of disease and cannot be used to prevent or treat gingivitis. Second-generation agents are characterized by both antibacterial activity and substantivity. Chlorhexidine was the first such agent to be discovered. Used twice daily, chlorhexidine is as effective as first-generation agents used five to seven times daily (*9*). Stannous fluoride may prove to be another second-generation agent; however, although it has good substantivity, it is not a potent antimicrobial agent.

MECHANISMS OF ACTION

Chlorhexidine and alexidine are the most thoroughly studied members of a class of compounds called the *bis*-biguanides. Studies have been made of the roles played by these agents in controlling plaque-dependent oral diseases such as caries and gingivitis. The structures of chlorhexidine and alexidine differ in the natures of the two R groups attached to the *bis*-biguanide residue (fig. 1). In chlorhexidine, the R groups are two chlorinated phenyl groups, but in alexidine the R groups are two saturated, aliphatic side chains. Most chlorhexidine solutions contain either its gluconate or acetate salt, since they are more soluble than the parent compound.

Chlorhexidine's *bis*-biguanide core is protonated within physiologic pH ranges, thereby assuming a high positive-charge density. These cationic properties form the basis for chlorhexidine's mode of action, substantivity, and effectiveness as an antiplaque agent (*10,11*).

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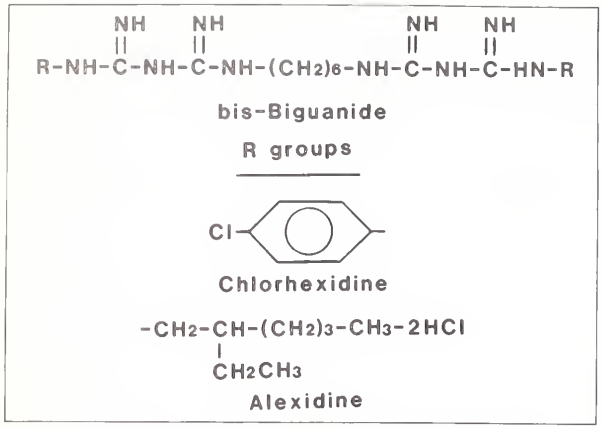

Figure 1. Structures of the *bis*-biguanides chlorhexidine and alexidine.

Interest has focused on chlorhexidine because it can be used at low concentrations (0.02%–0.20%) and because it is substantive, which extends its therapeutic effectiveness. Both properties arise from chlorhexidine's affinity for the hard and soft oral tissues. Its affinity for tooth surfaces is probably due to an attraction between the agent's high positive charge and the large number of negatively charged components (carbosyl, sulfate, and phosphate groups) found in salivary mucins within the pellicle component of the enamel-pellicle complex. Chlorhexidine may also have an affinity for the large number of negatively charged groups found in cell membranes. Chlorhexidine's affinity for negatively charged groups within the enamel-pellicle complex and on oral mucosal cell surfaces concentrates the agent from dilute rinse preparations. The affinity also explains how chlorhexidine is retained in the oral environment and released over an extended period.

The high positive-charge density of chlorhexidine is also responsible for its effectiveness as an antimicrobial agent and for its broad spectrum of activity against gram-positive and gram-negative bacteria, and fungal species. All of these classes of microorganisms have negatively charged groups on their cell surfaces. For example, the teichoic acids of gram-positive bacterial cell walls and many lipopolysaccharides on gram-negative bacterial cell surfaces contain great numbers of negatively charged phosphate groups. When chlorhexidine binds to the negatively charged microbial cell surfaces, it alters and ultimately disrupts the cell membrane. Cytoplasmic constituents then leak from the cell, eventually causing death.

ANTIMICROBIAL ACTIVITY

Chlorhexidine shows a broad spectrum of antimicrobial activity. It is potent against both gram-positive and gram-negative bacteria as well as against yeasts and fungal organisms (*10,13*). However, the agent is not effective against bacterial spores, viruses, or acid-fast bacteria such as *Mycobacterium tuberculosis*.

Although chlorhexidine has a broad spectrum of action, it is more effective against some types of microorganisms than against others. For example, gram-positive microorganisms are more susceptible than are their gram-negative counterparts. With respect to gram-negative organisms, isolates of *Escherichia coli* are more susceptible to chlorhexidine than are members of the genera *Proteus, Pseudomonas,* and *Klebsiella*.

Other factors add to chlorhexidine's effectiveness as an antimicrobial agent. Microorganisms completely resistant to chlorhexidine rarely emerge even after long-term use; succession by yeasts and other undesirable fungal species rarely occurs; and the sensitivity of specific components of the oral microflora to the agent is not significantly altered even after extended therapy (*10*).

CLINICAL STUDIES

The effectiveness of chlorhexidine as a plaque control agent is thought to be due to its structural properties (*10,11*). These properties include potent antimicrobial activity, effectiveness at low concentrations, substantivity, which prolongs the agent's therapeutic effects in the oral environment, little if any absorption from the gastrointestinal tract, which decreases the possibility of adverse systemic side effects, infrequent use in the treatment of systemic infectious diseases in human subjects, and the ability to reduce plaque scores, which allows the agent to effectively treat diseases of both the hard and soft dentition.

Chlorhexidine's potent, broad-spectrum antimicrobial action makes it effective in reducing both supragingival and subgingival plaque (*10,14–17*). The use of chlorhexidine in animals that were fed high-sucrose diets substantially reduced the incidence of caries compared with nontreated control groups (*10,12,18–20*). Also, a 3-year longitudinal study with Swedish schoolchildren who used chlorhexidine showed a significant reduction in both *Streptococcus mutans* counts and caries incidence compared with a nonchlorhexidine control group (*10,21*).

The use of chlorhexidine can improve the gingival health of human subjects even without oral hygiene. In studies with a human gingivitis model, Löe and Schiott (*22*) showed that rinsing twice a day with a 0.2% chlorhexidine rinse can prevent gingivitis. In addition, it was shown that these rinses also return inflamed gingival tissue to a healthy state (*10,22–25*).

In the treatment of periodontal disease, chlorhexidine also has been successfully used to control postoperative plaque, thereby decreasing the probability of infection, and to promote healing at surgical sites.

The oral use of chlorhexidine by human subjects has produced no serious systemic effects. In some instances, undesirable local effects are known to occur (*10,18,26,27*). The most common of these side effects is a yellow to brownish black staining of the teeth and certain types of restorations. Staining of the dorsum of the tongue is also a common side effect of chlorhexidine use. Stains on the teeth usually require professional cleaning. However, in contrast to the tooth stains, the tissue stain gradually disappears after the agent is discontinued. These staining effects depend partly on the patient's diet, on the concentration of the agent, and on the frequency and duration of use. Chlorhexidine can also alter the patient's sense of taste.

Serious systemic side effects from oral chlorhexidine use have not been reported, probably because the agent is not readily absorbed from either the mouth or the gastrointestinal tract. Since oral side effects have not been serious, the prudent, therapeutic use of chlorhexidine in the treatment of oral disease appears to be justifiable.

CLINICAL STUDIES IN CANCER PATIENTS

Chlorhexidine mouthrinses have been demonstrated to provide an improved antimicrobial approach to treatment of periodontal disease and other oral infections (*28–33*). If it is assumed that oral stomatitis in patients undergoing intensive antineoplastic treatments results largely from superinfection of a reversibly damaged mucosal barrier, appropriately timed use of topical chlorhexidine might be more effective prophylaxis against the oral complications of chemoradiotherapy than the measures traditionally employed (*34–40*).

Chlorhexidine mouthrinse use to aid in the control of oral stomatitis in patients undergoing intensive preconditioning or conditioning chemotherapy or radiotherapy has recently been evaluated in several studies. Clinical oral parameters for evaluation include the effects of chlorhexidine mouthrinse on one or more of the following: mucositis, gingival inflammation, dental plaque, dental stain, and candidiasis. Several of the studies also assessed one or more of the following microbiologic parameters by either incidence or quantity: total yeasts, *Candida* spp., total streptococci, and gram-negative bacilli. The effects of an increase or decrease in the oral infectious challenge by these pathogens have also been evaluated. A review of several studies performed by my colleagues and I at the University of Kentucky Medical Center and a discussion and comparison of other studies follows.

In a prospective, double-blind, randomized study, we examined the use of a chlorhexidine digluconate mouthrinse for prophylaxis against oral mucosal complication in 51 bone marrow transplant patients (*41,42*). Significant reductions in plaque and gingivitis scores were seen on days 33 and 60 for patients using the chlorhexidine rinse. At day 90, 30 days after discontinuation of chlorhexidine use, plaque and gingivitis scores in the chlorhexidine-treated group approached baseline levels. Plaque and gingivitis scores for control patients did not change throughout the study.

Extrinsic dental staining was similar throughout the study for both the chlorhexidine and control groups. A modest, although not significant, increase in dental staining was noted in both groups during the treatment. Chlorhexidine mouthrinse produced significant reductions in the incidence and severity of oral mucositis. Mucositis also resolved more quickly in patients receiving chlorhexidine. Concomitant reductions in total oral streptococci and oral *Candida* organisms were seen in the patients using chlorhexidine.

The number of patients on each examination day and the number and percentage of those who were positive for gram-negative bacilli in both the treatment and placebo groups was also examined. At each examination, including the baseline, a greater percentage of the patients receiving chlorhexidine had oral gram-negative bacilli than did individuals receiving the control rinse. Although the percentage of cultures positive for gram-negative bacilli was greater at each examination day in the chlorhexidine group than in the placebo group, there were no statistically significant differences between the groups. In addition, there were no significant differences between the two groups in the number of positive blood, urine, and throat cultures obtained during chlorhexidine use (*41,42*).

In a similar study (*43*), a 0.12% chlorhexidine digluconate mouthrinse (15 mL, three times a day) was evaluated in a prospective, double-blind randomized trial as prophylaxis against cytotoxic therapy-induced damage to oral soft tissues. Forty inpatients receiving high-dose chemotherapy and 30 outpatients receiving high-dose head and neck radiation therapy were evaluated. Chlorhexidine mouthrinse significantly reduced the incidence of oral mucositis in the chemotherapy group on day 14, day 21, and at 1 week of follow-up, on day 28. Mucositis in the chemotherapy patients on chlorhexidine also resolved more rapidly. Mucositis severity was significantly less than in the control chemotherapy group on day 14, day 21, and at 1 week of follow-up. Concomitant trends in the reduction in numbers of oral streptococci and yeasts were noted in the chemotherapy group receiving chlorhexidine mouthrinse.

In contrast, no differences were observed in oral mucositis between the control and chlorhexidine groups of high-dose radiotherapy patients (*43*). This finding may be partially explained by the observation that the chlorhexidine molecule, a divalent cation, probably does not bind directly to epithelial tissues but rather to negatively charged salivary mucins or glycoproteins (*44,45*). In vitro evidence further supports the concept that salivary glycoproteins are necessary cofactors for mucosal cell protection by chlorhexidine (*44,45*). In our experience, high-dose radiation therapy patients developed severe, persistent xerostomia rather quickly (i.e., within 14–21 days) after the initiation of radiation therapy, depriving oral epithelial tissues of their usual coating of salivary fluids and diminishing the potential mucosal protectant effect of chlorhexidine in these patients. Similar reductions of oral microflora to those seen in the chemotherapy population were also noted for radiation therapy patients receiving chlorhexidine. Although not significant, some increase in gram-negative bacilli was noted in the chlorhexidine-treated patients in both the chemotherapy and radiotherapy groups, but there was no correlation with increased systemic infection (*43*).

In order to determine whether the use of a chlorhexidine mouthrinse may predispose intensively treated patients to emergence of resistant strains of oral gram-negative bacilli, 15 bone marrow transplant patients who received three 0.12% chlorhexidine digluconate mouthrinses daily for 8 weeks were monitored weekly for the occurrence of oral opportunistic gram-negative bacilli (*46*). Tongue and buccal mucosa were sampled with Culturette swabs that were streaked on plates containing selective MacConkey agar. After incubation, colony-forming units were scored and putative gram-negative bacilli were classified by use of the API 20E (Analytab Products) rapid identification system and supplemental biochemical tests. After identification, the susceptibilities of all gram-negative bacilli to chlorhexidine were determined by means of a disk diffusion sensitivity assay. Ten (67%) of the bone marrow transplant subjects had at least one gram-negative bacilli-positive tongue culture, and eight (53%) had gram-negative bacilli in samples taken from the buccal mucosa. Of 218 samples taken, 26% and 24% from the tongue and buccal mucosa, respectively, were positive for gram-negative bacilli. The predominant clinical gram-negative bacilli isolates were *Enterobacter cloacae* (46%) and *Klebsiella pneumoniae* (30%). The minimum inhibitory concentrations (MICs) of chlorhexidine for these strains were similar to those for American Type Culture Collection reference strains. Although chlorhexidine MIC values for the clinical gram-negative bacilli isolates were high ($\leq$37.5 to $\leq$300 μg/mL), they were not dependent upon length of exposure to the agent. Therefore, changes in sensitivity or resistance to chlorhexidine did not

appear to occur. The results suggest that the mouths of bone marrow transplant patients—and perhaps of other immunosuppressed individuals—should be routinely monitored for gram-negative bacilli, as are other clinically important sites, such as the throat and the urinary and gastrointestinal tracts (*46*).

DISCUSSION

Numerous studies have reported the efficacy of chlorhexidine use in the prevention of local and systemic complications in bone marrow transplant and other immunosuppressed patients. Studies at the University of Kentucky have shown that daily chlorhexidine rinses significantly decrease gingivitis, stomatitis, and oral *Candida* levels, lower the incidence of candidiasis, and reduce *Candida*-related morbidity and mortality in bone marrow transplant patients (*41*). In addition, McGaw and Belch (*32*) have suggested that chlorhexidine rinses are effective in the prophylaxis of stomatitis and candidiasis in the myelosuppressed patient. Langslet et al. (*33*), successfully used topical 0.2% chlorhexidine to treat active pseudomembranous candidiasis in seriously ill children, most of whom were suffering from acute leukemia, and suggested that chlorhexidine be used prophylactically to maintain optimum oral health in these patients. Weisdorf et al. (*47*) recently reported that daily chlorhexidine rinses by bone marrow transplant subjects decreased the oral *Candida* colonization burden with time and cited a trend towards diminished oral candidiasis compared to a control group using a placebo rinse. Most studies dealing with use of chlorhexidine rinses in immunocompromised patients undergoing intensive chemotherapy have documented some degree of positive therapeutic effect with regard to one or more of the following parameters: stomatitis, gingivitis, oral *Candida* levels, candidiasis, candidemia, and *Candida*-related morbidity and mortality. However, two recent studies have shown the use of chlorhexidine not to be of benefit to patients undergoing high-dose head and neck radiation (*43,48*).

The relative effectiveness of chlorhexidine rinses has been reported differently by different studies. This may be due in part to differences within the studies themselves. Variations exist in the concentration of chlorhexidine used, the mode or frequency of chlorhexidine application, the duration of chlorhexidine use, whether standard oral hygiene procedures were continued or discontinued, the use of antifungal agents other than chlorhexidine in "control" groups, other therapeutic regimens (such as prophylactically administered acyclovir), and the use of oral and systemic broad-spectrum antibiotics. These differences may collectively serve to change the efficacy of chlorhexidine rinses. The literature supports the prophylactic use of chlorhexidine in severely immunosuppressed patients to obtain optimum oral health. Further studies should be done to determine what factors modulate its efficacy.

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Pretreatment Oral Health Care Interventions for Radiation Patients

William E. Wright

Individuals undergoing head and neck radiation treatments and cytotoxic chemotherapy for cancer are at risk for a variety of deleterious oral side effects. This added potential for oral problems places the cancer patient in a special category for oral health care management. Pretreatment intervention regimens directed at the supporting tissues of the teeth can effectively remove dental calculus deposits and cementum-imbedded bacterial toxins and reverse the inflammatory state of the periodontium back to normal. A variety of patient-applied fluoride agents are extremely effective in preventing severe radiation-associated dental decay, which is likely to occur after salivary gland dysfunction. Deficiencies in current patient management protocols and areas of current research are noted. Two essentials for a successful patient management program are emphasized: early referral of the patient to a knowledgeable dental team to ensure pre-cancer treatment oral health care intervention and long-term maintenance, and a family-oriented education and motivation program to enhance patient understanding and compliance. [NCI Monogr 9:57–59, 1990]

In developed countries, professionally delivered oral prophylaxis, i.e., calculus removal and tooth surface polishing, in concert with the individual's daily efforts to remove soft bacterial masses from the teeth, has long been the cornerstone of preventive periodontal health care. The use of topically or systemically delivered fluoride agents has also shown great benefit in the prevention and control of dental caries in healthy humans. Individuals undergoing head and neck radiation treatments and cytotoxic chemotherapy are at risk for a variety of deleterious oral side effects that place them in a special category for oral health care management. This article will describe and provide critical evaluation of the two general regimens mentioned above as they relate to proposed pre-radiation therapy interventions for oncology patients..

REGIMENS AFFECTING THE PERIODONTIUM

The rationale for the variety of mechanical oral hygiene procedures (calculus removal, root planing, soft tissue curettage, tooth surface polishing, and daily plaque removal) is to remove the local etiologic factors of periodontopathic bacteria and their toxins, which initiate inflammatory diseases of the periodontium. In the relatively healthy individual, resident periodontal pathogens may produce destructive inflammatory processes that can result in tooth mortality. In the immunosuppressed oncology patient, certain oral organisms may be lethal.

Clinical observation, animal research, and human clinical trials with microbial analysis and microscopic assessments of periodontal tissues have demonstrated that mechanical hygiene procedures can effectively remove calculus deposits and cementum-embedded toxins and reverse the inflammatory state of the periodontium to a more normal condition.

The positive effects of mechanical procedures on the periodontium include reduction or elimination of inflammatory cells in the gingiva, microulceration of the gingival sulcus epithelium, and vascular dilatation and leakage. The overall effect of mechanical procedures is the reversal and control of inflammation. There is little or no controversy that these positive effects on the periodontium are beneficial as pretreatment interventions for patients about to undergo oncology therapy.

Unfortunately, many individuals are not referred to an oral health care facility for pretreatment oral diagnosis and intervention. Thus, radiation therapy is initiated with incomplete knowledge of what oral side effects to expect and without benefit of currently available interventions. A second weakness in periodontal intervention programs is that most oral hygiene procedures are not specific. This weakness results from the lack of diagnostic modalities that can quickly, precisely, and at reasonable cost identify resident oral organisms that are potentially dangerous to the oral and general health of the oncology patient. Such improved techniques would allow the clinician to identify specific organisms, against which specific intervention modalities could be directed. The degree and duration of effectiveness of the intervention technique could also be monitored periodically. Current research emphasizes a variety of microbiologic assessments as well as diagnostic and treatment-effectiveness evaluation techniques for the periodontal diseases that affect otherwise healthy individuals (*1–5*). These studies are seeking associations between clinical parameters and the results of morphologic, immunofluorescence, DNA probe analysis, and other marker technologies. In addition, the identification of defects in a particular individual's immune defense mechanisms appears to be important in the diagnosis and treatment of certain pathologic conditions. New instruments and antimicrobial techniques should improve the effectiveness and effective duration of mechanical hygiene procedures and eventually replace them. Researchers and clinicians interested in oral oncology should adapt the more promising technologies to research, prevention, and treatment of oral problems in cancer patients.

REGIMENS AFFECTING THE TEETH

One of the long-term devastating effects of radiation therapy to the head and neck area is the direct alteration of salivary gland function, so that the quantity and quality of saliva are diminished. These alterations in saliva contribute to changes in the oral environment that can result in severe radiation-induced dental caries.

In the early 1960s, researchers at the National Institute of Dental Research introduced the application of fluoride gel via custom-constructed vinyl trays to the teeth of experimental

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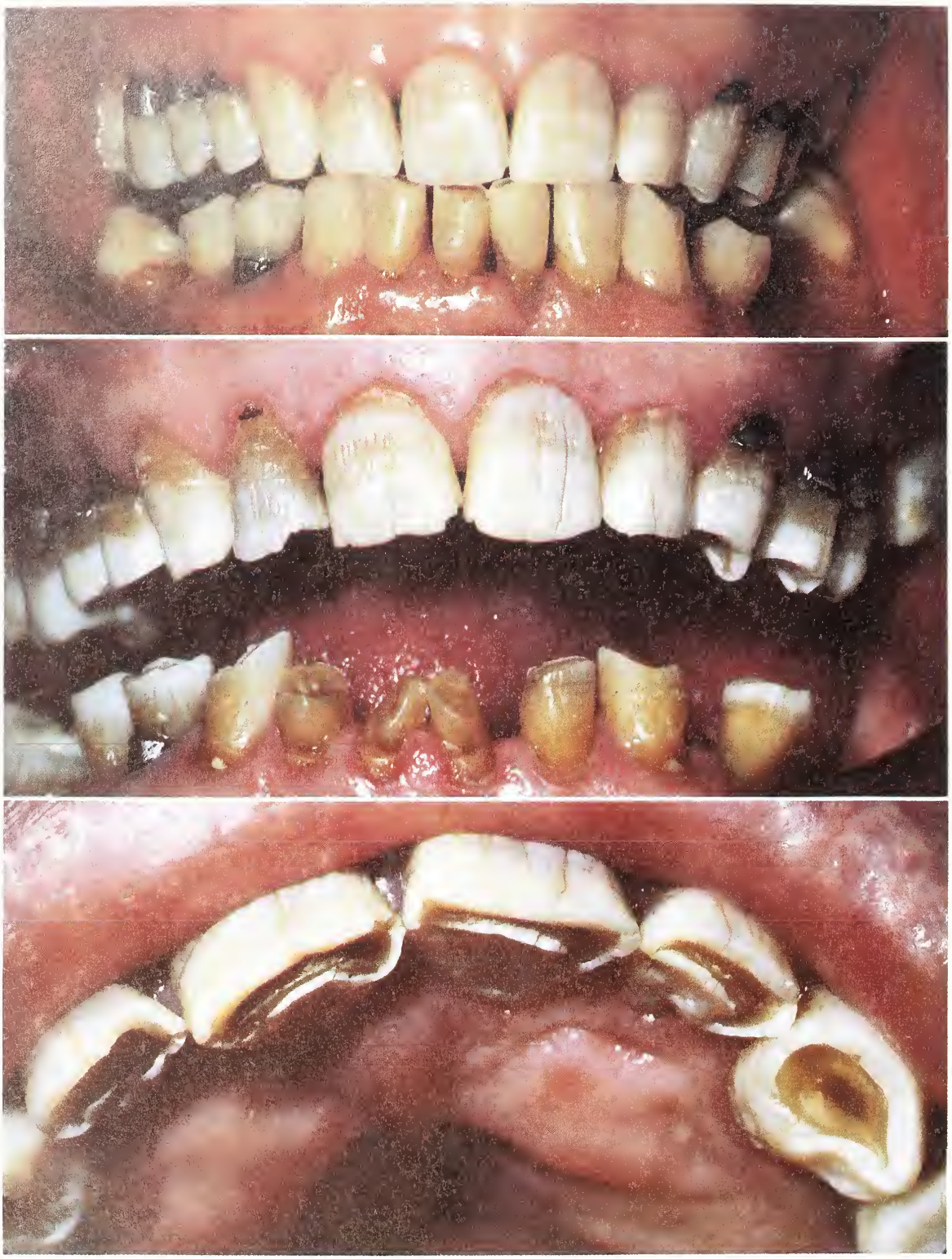

Figure 1. (Top) Pre-head and neck radiation oral condition of 66-yr-old male, demonstrating satisfactory dental restoration and no existing enamel defects. (Middle) Same subject 12 yr after radiation (6,400 rads) to head and neck for oral cancer. Note severe enamel dissolution of both maxillary and mandibular teeth. (Bottom) Same subject, demonstrating severe loss of incisal enamel and progressive abrasion into dentin. Both acidulated and nonacidulated fluoride agents were used long term to prevent caries

animals to control tooth decay. That technique has remained the standard treatment for the prevention and control of radiation-associated dental caries (*6,7*). Similar regimens have been demonstrated to be extremely effective if the radiation patient is sufficiently motivated to comply for extended periods of time —perhaps even for a lifetime.

Unfortunately, it is difficult to get radiation patients to comply with the use of fluoride and vinyl delivery trays for the long term. This technique is also moderately expensive due to time required by dental professionals and the laboratory technician to construct the trays. A second weakness involves a lack of knowledge about which fluoride agents and what concentrations are most effective and economical for preventing and controlling radiation-associated dental caries.

In 1985, a program developed at the National Institute of Dental Research dental clinic for enhancing the oral health care of cancer patients undergoing oncology therapy was described (*7*). The deleterious oral side effects associated with oncology treatments are demonstrated, and regimens to be provided by the dental team or self-administered by the patient are described. This program is based on the philosophy that patient motivation is essential for the cooperation and compliance required to preserve oral health during and after medical treatments.

A group of subjects undergoing radiation treatments to the head and neck are now being studied to assess the value of the formal patient education program described above. The ability of three commercially prepared fluoride products to prevent caries after topical application via custom-fabricated vinyl trays, brushing, or rinsing is also being assessed. Caries scores, patient education questionnaires, compliance differences, and periodontal parameters are being evaluated.

A variety of delivery methods for oral health care products are currently being researched. Slow-release mechanisms may make compliance unimportant (*8*). Oral rinses, sprays, and brush-on products may prove effective and encourage greater compliance than current techniques (*9,10*).

With the strong emphasis on dental caries prevention and control, another area of tooth protection seems to have been neglected. The teeth of subjects with salivary gland dysfunction exhibit, in time, an apparent "dessication" of enamel and weakening of supportive structure so that progressive abrasion, incisal chipping, and facial surface attrition occur (fig. 1). It is important to learn whether this problem is directly related to salivary changes or whether the changes are linked to long-term fluoride use. In this area, the potential importance of remineralizing solutions and "calcifying fluids" in protecting the tooth surfaces of radiation-treated individuals should be explored (*11*).

SUMMARY

Intervention regimens are currently available for preparing both the periodontium and the teeth before head and neck radiation treatment. However, greater emphasis needs to be placed on referral of individuals to a competent dental team.

Improved diagnostic and intervention assessment techniques related to periodontal pathogens are needed so that prevention and control regimens can be specifically targeted.

Anticaries protocols that make use of topically applied fluoride agents can be effective if the patient is properly motivated. Effective information and motivation programs need to be provided for oncology patients.

Additional research is needed to establish what agents and concentrations are most efficacious and cost effective and to establish delivery techniques for the prevention of tooth surface destruction that will increase patient compliance.

The ultimate goal is to eliminate the deleterious oral side effects associated with oncology treatments.

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Pretreatment Strategies for Infection Prevention in Chemotherapy Patients

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It is important to understand the pathogenesis of acute oral infections in patients with chemotherapy-induced myelosuppression in order to develop strategies to prevent such complications. Four distinct oral sites that can either be acutely infected or contribute to acute systemic infection are the oral mucosa, dental pulp and periapical tissues, periodontium, and salivary glands. Many cytotoxic drugs can be directly stomatotoxic to replicating oral mucosa. Once mucosal integrity is affected, secondary acute infection can occur. Even without clinical ulceration, deleterious shifts in the oral microbial population can develop. Gram-negative bacilli have been identified as frequent colonizers of myelosuppressed patients, although coagulase-negative staphylococci are being recovered with increasing frequency. Strategies to prevent oral mucosal infection include reducing trauma and preventing proliferation of organisms. Dental pulpal infection is most commonly caused by extensive dental caries. Most pulpal infection is of bacterial origin and can progress to involve the periapical tissues of the involved tooth if not treated. Specific endodontic interventions will usually stabilize or eliminate the source of the infection until the patient's hematologic status returns to normal and definitive pulpal therapy can be provided. In part because acute pulpal complications in the myelosuppressed cancer patient are relatively infrequent, research on the causative organisms and the appropriate therapy of acute, systemic infection of pulpal origin has been limited. Many adults have chronic, asymptomatic periodontal disease. In its advanced stages, extensive ulceration may be present that is not clinically observable. In patients with reduced host defenses, exacerbation of preexistent periodontal disease can have systemic sequelae and is associated with elevated levels of periodontopathic organisms or pathogens typically associated with systemic infection in myelosuppressed cancer patients. Mechanical and chemical antimicrobial techniques are available to reduce prevalence and improve patient comfort and oral hygiene. Dental extractions may be indicated to eliminate the nidus of infection of either pulpal or periodontal origin in patients who are scheduled to receive myelosuppressive chemotherapy. Data indicate that such procedures may be performed without undue risk. Unlike patients who undergo bone marrow transplantation or radiotherapy, patients who receive chemotherapy do not commonly experience subjective salivary gland dysfunction. Occasionally, a transient xerostomia may occur; this condition is frequently attributed to the patient's oral habits, such as breathing through the mouth. The dessicating effect of breathing through the mouth can contribute to oral mucosal injury during function as well as provide a setting for acute infection of commensal origin. More research is needed on the effects of chemotherapy on salivary host defenses. [NCI Monogr 9:61–71, 1990]

Infection prevention is an optimal goal in the management of the myelosuppressed chemotherapy patient (*1–3*). Although the need to begin chemotherapy and to comply strictly with prophylactic measures can complicate the clinical course of the patient, successful infection prevention can reduce morbidity and mortality.

Strategies for prechemotherapy prevention of acute infections involving four oral sites are described: the oral mucosa, dental pulp and periapical tissues, periodontium, and salivary glands. As appropriate, preventive interventions that begin prior to chemotherapy and continue during myelosuppression are also discussed.

ORAL MUCOSA

The cytotoxic effects of chemotherapy on replicating oral mucosal cells can result in severe oral mucositis (*4–6*). The patient feels a mucosal "burning" sensation within 1 week of administration of the drugs; the mucosa may appear erythematous. The lesion subsequently ulcerates, either remaining focal or becoming widespread. The histologic changes associated with these clinical findings most commonly include collagen degeneration, minor salivary gland degeneration, epithelial atrophy, and dysplasia (*7*). Once ulcerated, the oral mucosa can become secondarily infected during granulocytopenia. Thus, drug-induced mucositis represents a portal of entry for systemic infection.

Drugs that typically cause oral mucositis include methotrexate, doxorubicin, 5-fluorouracil, and bleomycin. Although it is difficult to predict which patients receiving these drugs will develop mucositis, many studies suggest that poor oral hygiene is a contributing factor (*8–13*). Also, in our experience at the University of Maryland, it appears that patients who experience mucositis during one course of chemotherapy will often experience mucositis of similar extent and location during subsequent courses of the same regimen. The lesions typically last for 10–14 days after cessation of chemotherapy. The sites most commonly involved include the tongue and buccal and labial mucosa, although the oropharyngeal mucosal surface may be generally ulcerated.

Deleterious shifts in the microflora can occur without initial clinical evidence of mucosal ulceration; surveillance cultures of acute nonlymphocytic leukemia (ANLL) patients, including those of the oral mucosa, reveal that multiple pathogens can be

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acquired while the patient is hospitalized. Common pathogens include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* (*1–3*). In addition, a shift to primarily gram-negative enteric bacilli (GNB) colonizing the oropharynx may occur in hospitalized patients (*14,15*); the oral flora changes from chiefly aerobic and anaerobic gram-positive cocci and bacilli to a flora in which gram-negative organisms predominate. Broad-spectrum antibiotic therapy can result in even further shifts to more resistant bacteria or to fungi such as *Candida* spp. and *Torulopsis glabrata* (*1,3*). Most infections in the compromised host are caused by organisms that have been colonizing at or near the site of infection (*16*).

Multiple topical and systemic approaches have been used to prevent mucosal infection in the granulocytopenic cancer patient (*17,18*); such interventions are listed in table 1. These strategies either have been shown to be effective in controlled studies or are justifiable at the empiric level; selection of cooked foods of low microbial content to reduce acquisition of new organisms is an example of the latter category. Several of these approaches overlap; for example, rates of acquisition of nosocomial organisms can be affected by various protocols for gastrointestinal decontamination currently in use. The last three approaches in table 1 have not generally proven to be effective in humans; however, granulocyte colony-stimulating factor is now being explored in chemotherapy patients.

The prevention and treatment of chemotherapy-induced mucositis and infection have not been uniformly successful. Reduction in the severity or duration of mucositis by chlorhexidine and other oral rinses has been reported for cancer patients (*19–24*). Table 2 summarizes key references specifically reporting on the efficacy of chlorhexidine mouthrinses in either preventing or treating acute mucositis and oral candidiasis in these patients. Sharon et al. (*25*) reported that among nine leukemic patients who were carriers of *Candida albicans*, there was no significant decrease in titers of this organism following daily oral rinses with 0.2% chlorhexidine; this was an open-label, noncontrolled clinical trial. None of these patients had overt oral candidal lesions. In contrast, however, the investigators reported that low concentrations of chlorhexidine decreased the titer of *C. albicans* in vitro. McGaw and Belch (*19*), in a double-blind, placebo-controlled prophylactic trial, reported reduced mucositis scores during remission induction; they suggested that 0.1% chlorhexidine mouthrinses may be of value in the prevention of oral candidiasis in the myelosuppressed leukemic patient.

Table 1. Strategies for mucosal infection prevention in granulocytopenic cancer patients

Reduction in mechanical and thermal trauma
Reduction in acquisition of new organisms
Gastrointestinal decontamination
Selective decontamination/colonization preservation
Protected environments and other isolation techniques
Antifungal prophylaxis
Antiviral prophylaxis
Passive immunization
Active immunization[a]
Granulocyte transfusions[a]
Immunoregulatory reagents[a]

[a]Questionable efficacy to date, with exception of granulocyte colony-stimulating factor.

In 1988, Ferretti et al. (*22*) reported effective prophylaxis of oral mucositis and candidiasis with 0.12% chlorhexidine rinses in 51 bone marrow transplant patients. This study was a double-blind, prospective, placebo-controlled trial. In contrast, a recent study by Weisdorf et al. (*26*) with 100 marrow transplant recipients did not reveal similar results; in this study, however, prophylactic acyclovir was not routinely used, and compliance with the schedule of chlorhexidine doses was 71.8%. Spijkervet et al. (*27*) recently reported a prospective, placebo-controlled, double-blind prophylactic trial of 30 patients undergoing radiation therapy for head and neck cancer; 0.1% chlorhexidine oral rinses administered 4 times daily for 5 weeks were not successful in either suppressing oral flora (except for *Streptococcus viridans*) or lowering the incidence or severity of oral mucositis. However, these patients received radiotherapy, not chemotherapy. The study of Park and Park (*28*), an open-label investigation in BALB/c mice without cancer, suggested that 0.2% chlorhexidine may moderately reduce the replication rate of herpes simplex virus type 1 (HSV-1). The significance of these results for HSV-1 infection in humans is still uncertain. The authors are currently studying the combined effectiveness of acyclovir and chlorhexidine against this virus; the high efficacy and low toxicity of acyclovir prophylaxis, however, may render such combined strategies unnecessary.

A variety of other topical oral rinses, including benzydamine hydrochloride (*21*), beta-carotene (*23*), and allopurinol (*24*), have been reported to be effective in reducing the incidence of chemotherapy- or radiation-induced oral mucositis (table 3); in contrast, oral sucralfate suspension was not found to be effective in prevention and treatment of oral mucositis in 48 pediatric patients receiving chemotherapy for newly diagnosed ANLL (*29*). Larger prospective, double-blind, placebo-controlled trials should be considered for these drugs.

Studies to reduce the duration and severity of oral mucositis and infection are important, since approximately 47% of all acute infections arising in patients with ANLL are of nosocomial origin (*16*). When they develop in a patient who is debilitated by both disease and chemotherapy, these infections are life-threatening; for example, infection is the leading cause of morbidity and mortality in patients with ANLL (*1,3,30*). The oral mucosa of the cancer patient can readily become acutely infected by a variety of organisms, particularly when a break in mucosal integrity occurs because of the direct stomatotoxic effects described above. For example, in one study of hospitalized patients with acute or chronic leukemia in the blastic phase, the oral infection rate was 32.9% (*31*). Of these oral infections, approximately 52% were fungal and 15% were caused by HSV-1. In a related study, solid-tumor patients who experienced less intense myelosuppression and stomatotoxicity had an oral infection rate of 10%, yet developed oral fungal infections at a frequency of 69% and HSV-1 infections at 11% (*32*).

As suggested by the data above, *Candida* infection is the most common oral fungal infection in myelosuppressed cancer patients (*33*). The most frequent sites of oral candidiasis are the tongue, mucosa (palatal, buccal, and gingival), and the lip commissures. The clinical appearance of oral candidiasis varies but is typically described as raised, white, "curdy-looking" lesions. The lesions are often painful and, when abraded, are

Table 2. Studies of chlorhexidine in cancer populations

Authors (ref. No.)	Subjects (No.)	Outcome
Sharon et al.[a] (*25*)	Chronic leukemia (9)	In vivo: no significant decrease in *C. albicans* titer; in vitro: marked decrease in *C. albicans* titer
McGaw and Belch (*19*)	Acute leukemia (16)	Reduced mucositis scores for weeks 3 and 4; effective prophylaxis of oral candidiasis (?)
Ferretti et al.[a] (*20*)	BMT: aplastic anemia (1); acute leukemia (2); chronic leukemia (1)	Clinical resolution of existing oral mucositis
Ferretti et al. (*22*)	BMT: acute leukemia/lymphoma (28); chronic leukemia (*20*); myelodysplasia (1); nonneoplastic disorders (2)	Effective prophylaxis of oral mucositis and candidiasis
Weisdorf et al. (*26*)	BMT: acute leukemia (52); chronic leukemia (27); aplastic anemia (9); other disorders (12)	No therapeutic advantage except for possible efficacy in controlling risk for candidiasis
Spijkervet et al. (*27*)	Head and neck cancer–radiation (30)	No overall reduction in oropharyngeal flora or mucositis
Park and Park (*28*)	Murine model[b] (51), Vero cell monolayer	Moderate in vivo and in vitro reduction in HSV-1 replication

[a]Open-label, noncontrolled trial.
[b]Open-label trial in BALB/c mice without cancer.

ulcerated. Fungal dissemination can occur through the ulcerated mucosa. Prophylaxis with agents such as clotrimazole has not been optimal in leukemic patients; this drug, however, has shown efficacy in renal transplant recipients and patients with solid malignant tumors (*34*).

Viral infection following chemotherapy (*35–37*) or bone marrow transplantation (BMT) (*38–41*) can result in considerable oral disease. Viral infections, particularly in BMT patients, are predominately caused by HSV, varicella-zoster virus, and cytomegalovirus (*40*). Oropharyngeal viral infection can cause marked patient discomfort, interfere with normal oral function, and cause death. HSV-induced mucositis can be easily confused with oropharyngeal mucositis secondary to the direct stomatotoxic effects of either induction drugs or conditioning chemoir-radiation regimens used prior to BMT. Early recognition of HSV infection is important, since the infection can often be successfully managed with acyclovir (*42*). Patients identified as being at risk for HSV mucositis may benefit from acyclovir prophylaxis (*43*). However, acyclovir-resistant HSV strains have been reported for some patients (*44,45*).

Table 3. Reduction in incidence or severity of oral mucositis

Authors (ref. No.)	Patient population (No.)	Intervention
Prada and Chiesa[a] (*21*)	Head and neck cancer (36)	Benzydamine hydrochloride
Mills[a,b] (*23*)	Oral squamous cell carcinoma (20)	Beta-carotene
Shenep et al.[c] (*29*)	Acute nonlymphocytic leukemia (48)	Sucralfate
Tsavaris et al.[d] (*24*)	Gastrointestinal cancer (16)	Allopurinol

[a]Chemotherapy and/or radiotherapy patients.
[b]Nonblinded, randomized trial.
[c]Limited efficacy in prevention and treatment of oral mucositis in children and adolescents.
[d]Open-label, noncontrolled trial.

Recognition of the factors that predispose patients to HSV infection helps identify the myelosuppressed patients who might benefit most from antiviral prophylaxis or other approaches to prevention of HSV reactivation. My colleagues and I retrospectively analyzed factors associated with acute oropharyngeal HSV infection among 627 patients who had undergone allogeneic BMT for leukemia, lymphoma, or aplastic anemia (*41*). Of the 627, 233 (37%) developed HSV infection; all but two were seropositive for HSV prior to transplant. Sixty-two percent of the seropositive patients had at least one episode of HSV reactivation during the first 100 days following transplant. Other factors that placed patients at increased risk for HSV infection were a pretransplant diagnosis of leukemia, being in remission at the time of transplant, and having been conditioned for transplant with chemoradiotherapy.

Factors other than bone marrow suppression can contribute to development of oral infections. For example, removable prostheses can increase the risk of infection in two ways (*46*). First, ill-fitting appliances can abrade the mucosa, already impaired by the toxic effects of the chemotherapy; this mechanical irritation can result in further ulceration. Second, appliances soaked in denture cups containing water or some denture disinfectants can readily become colonized with a variety of pathogens, including *P. aeruginosa, E. coli, Enterobacter* spp., *S. aureus, Klebsiella* spp., *T. glabrata,* and *C. albicans* (*47*). Careful attention to denture adaptation and soaking solutions is therefore mandatory for infection prevention; with proper care, the beneficial effects of enhanced appearance, nutrition, and self-image can be preserved for the chemotherapy patient by permitting restricted denture use during cancer treatment (*48*).

DENTAL PULPAL AND PERIAPICAL TISSUES

Prevention strategies for dental pulpal and periapical infection are also important (*46*). These infections are most commonly associated with extensive dental caries, a bacterial infection. Acute pulpal and periapical infections appear to occur

less frequently than other acute oral infections in patients undergoing remission induction; there are, however, few studies that analyze risk for or causative organisms in these infections in chemotherapy patients. Conversely, noninfectious periapical pathoses, such as leukemic infiltrate, can mimic acute periapical infection (*49*).

Many cancer centers have adopted empiric guidelines for prevention of pulpal and periapical infections during myelosuppression; the guidelines used at the University of Maryland Cancer Center are shown in table 4. Any patient who is scheduled to receive myelosuppressive chemotherapy should be evaluated orally, with careful attention to deep carious lesions and periapical disease. Pulpal pathosis can be evaluated with a thorough history, radiographs, and thermal testing in which hot or cold stimuli result in lingering pain, suggestive of irreversible pulpitis. Traditional diagnostic approaches (with the exception of percussion in the granulocytopenic patient) are thus used to determine pulpal status. Following diagnosis, pulpal therapy can be performed before initiation of chemotherapy. Acutely infected pulpal tissue (most commonly secondary to carious involvement) can be difficult to manage in the myelosuppressed patient; because of direct communication of the dental pulp with the systemic circulation, pathogens can disseminate readily.

Patients requiring chemotherapy occasionally present with pulpally infected teeth that cannot be restored and should be extracted; however, there may not be sufficient time for healing before the onset of myelosuppression. Judicious management may call for pulpal therapy to eliminate the acute infection prior to myelosuppressive therapy; extractions can then be performed when the patient's hematologic status returns to normal. On occasion, however, extractions for reasons of severe pulpal or periodontal infection must be performed prior to chemotherapy. To develop guidelines for such procedures, we studied 28 consecutive patients with ANLL admitted to the Cancer Center with indications for the extraction of teeth (*50*). The indications for extraction included severe periodontal disease or evidence of pulpal necrosis with resultant periapical pathology. Each of the following was used as a criterion for severe periodontal disease involving a tooth: a periodontal pocket >6 mm apical to the cemento-enamel junction (determined by a periodontal probing), and radiographic evidence of dissolution of alveolar bone. Both radiographic and clinical findings were used as criteria for pulpal necrosis and resultant periapical pathologic conditions. Radiographic evidence of dissolution of the lamina dura was used as an indication of periapical pathosis. This observation was evaluated in conjunction with positive clinical findings, which included sensitivity to percussion in a setting of >2,000 granulocytes/mm^3 or lack of response to an electric pulp tester.

Specific surgical guidelines were followed (table 5). The extraction was as untraumatic as possible, and included alveolectomies as necessary and primary closure with multiple interrupted sutures. When possible, the extraction was performed 10 days before the patient's granulocyte count fell to <500/mm^3. This meant that the extraction had to be done 3–4 days before chemotherapy was started. If this time was not available, the extractions were usually delayed until after chemotherapy when the granulocyte count rose to the required level. No hemostatic packing agents were placed in any extraction site. If the platelet count was <40,000/mm^3, random donor or histocompatibility-matched platelets (as available) were transfused 30 minutes before surgery in an attempt to obtain platelet counts of 40,000/mm^3 or greater at the time of surgery. If the absolute granulocyte count was <2,000/mm^3 on the day of extraction, a prophylactic antibiotic regimen of ticarcillin (75 mg/kg intravenously, 30 min preoperatively, repeated 6 hr postoperatively) and amikacin (150 mg/m^2 intravenously, 30 min preoperatively, repeated 6 hr postoperatively) was used.

One hundred nineteen extractions were performed. All patients were followed postoperatively for evidence of bleeding and acute infectious episodes until they either attained remission or died. There were no serious adverse sequelae, including wound breakdown or infection (table 6); the prevalence of other adverse effects was comparable to that in nonleukemic patients. While other centers may use somewhat different guidelines, this approach has been successful in our institution. It is concluded that, with proper precautions, extractions can be performed safely in these patients.

PERIODONTIUM

Chemotherapy patients with chronic periodontal disease may develop acute periodontal infections with associated systemic sequelae during episodes of granulocytopenia (*51–55*). It is important to understand the nature of periodontal floral shifts in these patients in order to develop approaches to reduce risk for acute periodontal infection. In 1986, my colleagues and I (*56*) reported a study examining the possibility that the magnitude of the quantitative microbial load at the sample site was associated positively or negatively with a shift in the level of GNB in myelosuppressed cancer patients (table 7). Data from both supra- and subgingival specimens were combined in this determination. Statistical tests revealed no significant intrapopulation differences when pre- and midchemotherapy values were compared in both the ANLL and small cell lung carcinoma (SCC) patients. In general, no significant interpopulation differ-

Table 4. Empiric guidelines for endodontic care in patients scheduled to receive myelosuppressive chemotherapy[a]

Diagnosis	Management
Reversible pulpitis	Caries control
Irreversible pulpitis	Initial biomechanical preparation of canal(s); temporary double closure
Necrotic pulp with chronic periapical pathosis	No endodontic treatment unless patient has 7 days from completion of endodontic therapy to onset of myelosuppression (<1,000 granulocytes/mm^3)
Necrotic pulp with acute periapical infection	Endodontic therapy or extraction, depending on systemic status of patient and scheduling of chemotherapy

[a] Modified from Peterson (*46*).

Table 5. Guidelines for dental extractions

Primary wound closure with multiple interrupted sutures
Ten days between extraction date and granulocyte count <500/mm^3
Avoidance of intra-alveolar hemostatic packing agents
Platelet transfusion if platelet count <40,000/mm^3
Prophylactic antibiotics if granulocyte count <2,000/mm^3

Table 6. Surgical procedures for ANLL patients[a]

Patient status	No. of patients	No. of extractions				
		Total	Mean/patient	Surgical	Alveolectomies	Complications
Complete remission	8	40	5	2	9	1
Admitted for treatment at granulocyte count:						
$>2{,}000/mm^3$	5	22	4.4	8	1	0
$\leq 2{,}000/mm^3$	15	57	3.8	3	7	0

[a]From Overholser et al. (*50*).

ences were found when ANLL pre- and midchemotherapy values were compared with the same SCC values; the only exception was that the total number of colony-forming units in oral rinse specimens from ANLL prechemotherapy patients was significantly lower than in SCC prechemotherapy oral rinse specimens [34 (± 43)$\times 10^4$ versus 234 (± 215)$\times 10^4$; $P=0.02$ (means $\pm$ SD)]. Large intersubject variations were observed, as reflected in the high standard deviations typical of oral culture findings when individual sites are analyzed.

Evaluation of proportional recovery was conducted in an attempt to recognize shifts in GNB populations during midchemotherapy. More than 50% of the patients in both populations showed no or very low level shifts. No intra- or interpopulation comparisons showed significant differences. GNB shifts to levels higher than 0.09% of the cultivable flora in individual subjects usually occurred at all sites sampled, and the quantitative values of cultivable flora at those sites were lower than those of flora at sites displaying minimal or no shifts. The value of 0.09% GNB was arbitrarily selected as indicative of abnormally high concentrations of these bacteria; this definition was based on culture studies of dental plaque in healthy individuals (*57–59*). Midchemotherapy GNB shifts tended to occur at sites where the total number of cultivable microflora decreased relative to prechemotherapy levels.

A portion of the GNB recovered from ANLL midchemotherapy cultures were characterized in an effort to account for commonly recovered species. Most of the isolates were *Pseudomonas* spp., but *P. aeruginosa* accounted for only 2.9% of these isolates. The latter species did not appear on Pseudocel agar in any of the specimens evaluated. The isolates identified, expressed as a proportion of the total isolates, were *Pseudomonas pickettii*, 58.8%; *Pseudomonas stutzeri*, 14.7%; *Pseudomonas maltophilia*, 5.9%; *Klebsiella pneumoniae*, 5.9%; *Pseudomonas cepacia*, 2.9%; *P. aeruginosa*, 2.9%; and *Alcaligenes* spp., 2.9%.

Surveillance cultures of gingival tissue constitute the previous experimental evidence showing the succession of GNB in the mouth during immunosuppression (*60*). This procedure entails streak inoculation of selective agar with cotton swabs of the attached gingivae. Our effort (*56*) differed from this previously described technique by targeting specific oral sites and providing quantitation of the predominant flora at the time of admission to the hospital and at the midpoint of myelosuppressive chemotherapy. Our study (*56*) showed that less than half of each population were colonized by high levels of GNB. Unaffected patients harbored facultative GNB at either low or undetectable levels. Approximately half the sites of affected ANLL patients were colonized at low levels ($<0.09\%$ of the total viable-cell count) and half were not colonized by coliforms before chemotherapy.

The sources of GNB are both endogenous and exogenous. Exogenous sources include food, water the hands of hospital personnel, sinks, and hospital apparatus such as respirators (*1,3,60*). A high percentage of hospitalized cancer patients acquire *P. aeruginosa* and *Klebsiella* spp. after hospitalization (*14,61*) and frequently develop acute infections with these organisms (*16*). The use of stringent infection control measures has markedly reduced the acquisition and prevalence of infections caused by exogenous pathogenic GNB and other microorganisms (*60*). The indigenous alimentary tract flora may pro-

Table 7. Recovery of GNB and total cultivable microflora from oral sites in cancer populations[a]

Population and sample (No. of samples)	Mean total microflora (10^4) $\pm$ SD		Mean GNB (10^2) $\pm$ SD		GNB as % of total	
	Prechemotherapy	Midchemotherapy	Prechemotherapy	Midchemotherapy	Prechemotherapy	Midchemotherapy
ANLL patients						
Molar supragingiva (18)	1,055 $\pm$ 1,931	261 $\pm$ 650	3.5 $\pm$ 7.5	721 $\pm$ 2,874	0.02	7.60
Molar subgingiva (18)	301 $\pm$ 474	211 $\pm$ 513	69 $\pm$ 282	113 $\pm$ 470	0.90	1.40
Oral rinse (9)	34 $\pm$ 43	16 $\pm$ 30	0.6 $\pm$ 1.4	8.8 $\pm$ 18	0.19	7.90
SCC patients						
Molar supragingiva (16)	775 $\pm$ 1,126	513 $\pm$ 762	0.9 $\pm$ 1.6	263 $\pm$ 727	0.03	3.20
Molar subgingiva (16)	352 $\pm$ 640	208 $\pm$ 384	1.1 $\pm$ 2.7	7.0 $\pm$ 15	0.04	0.80
Oral rinse (8)	234 $\pm$ 215	200 $\pm$ 302	1.8 $\pm$ 4.1	28 $\pm$ 55	0.06	0.23

[a]From Minah et al. (*56*).

vide colonization resistance to potential pathogens; strategies to preserve alimentary tract anaerobes have been reported (*3,17,62–64*).

In summary, specific oral sites in fewer than half the ANLL and SCC cancer patients showed quantitative and proportional increases in normally nonindigenous facultative GNB during myelosuppressive regimens. All oral sites were usually colonized by these bacteria in affected patients, but most sites did not harbor the organisms before chemotherapy. Antibiotic administration and reductions in the levels of indigenous microflora may have contributed to the succession of coliforms. In ANLL patients, nonpathogenic *Pseudomonas* spp. were the most commonly recovered isolates, but pathogenic species were detected.

My colleagues and I (*65*) also recently examined the specific relation of periodontal disease to qualitative and proportional shifts in the oral microflora of 21 ANLL patients [seven males and 14 females; mean age, 51.0 yr (range, 25–81)] observed during standardized myelosuppressive regimens (table 8). Supra- and subgingival microbial plaque specimens were individually collected from two contralateral molar sites in each participant at hospital admission (day 1) and during the point of maximal myelosuppression (day 14). Periodontal disease indices obtained at day 1 included site-specific measures of attachment loss and clinical assessment of disease status. By using a residualized change score analysis, periodontal disease status and attachment loss were positively correlated with increases in the proportional recovery of *Staphylococcus* spp. from supragingival sites and total yeasts from supra- and subgingival sites. When age-related covariation in the microbial shifts was controlled in the analysis, periodontal disease status and attachment loss demonstrated no significant correlation with increases in total yeasts at supragingival sites.

These findings suggest that host factors such as periodontal disease may contribute to patterns of oral microbial successions during cancer chemotherapy. In particular, host environmental factors such as periodontal attachment levels may be important in the preservation of oral indigenous flora. In this study (*65*), we found that attachment loss and periodontal disease classification at hospital admission were correlated with shifts in several pathogens during chemotherapy. Specifically, higher site-specific levels of attachment loss and more severe clinical assessments of periodontal disease status were associated with increases in proportional recoveries of both *Staphylococcus* spp. and yeast species within supragingival or subgingival plaque specimens or both at this sampling time. Enteric bacilli and staphylococci were presumed to be members of the plaque ecosystem because of their frequent and high-level occurrence in both supra- and subgingival samples of individual teeth that were sampled separately. Contaminants would be expected to be present in the supra- but not the subgingival plaques.

In a related study (*54*), we analyzed the subgingival microbial flora associated with 27 acute exacerbations of preexistent periodontal disease in 24 patients with chemotherapy-induced myelosuppression (tables 9 and 10). All but two acute periodontal infections developed when the patients had low granulocyte levels ($<1{,}000/mm^3$). Suspected pathogens were detected in high concentrations in subgingival plaque specimens in 17 episodes of acute periodontal infection; a single pathogen was recovered in 10 acute infections, and more than one pathogen was recovered in seven acute infections. *Staphylococcus epidermidis, C. albicans, S. aureus,* and *P. aeruginosa* predominated, with combinations of these detected in some patients. Concomitant bacteremia developed in two of these patients. The subgingival microflora associated with 10 acute periodontal infections was characterized by predominately indigenous microorganisms, which in nine episodes were in abnormal proportions compared with microbial profiles in noncancer patients with similar degrees of periodontal disease. These data demonstrate that pathogens normally associated with infections in myelosuppressed cancer patients, as well as indigenous oral flora, are associated with acute periodontal infections during granulocytopenia. This finding is important, since the periodontium site has not commonly been recognized as a source for acute infection in these patients. Despite the extent of acute infection, erythema and other inflammatory signs were typi-

Table 8. Relative distribution of indigenous and acquired bacteria before and during myelosuppressive chemotherapy in ANLL patients[a]

	Mean % of total viable cells ± SEM[b]			
	Supragingival plaque		Subgingival plaque	
Microflora	Prechemotherapy	Midchemotherapy	Prechemotherapy	Midchemotherapy
GNB	2.1 ± 1.7	16.6 ± 7.4*	3.1 ± 2.7	14.4 ± 7.5*
Fusobacterium nucleatum	4.2 ± 1.6	11.4 ± 7.2	7.2 ± 3.9	12.5 ± 7.6
Black-pigmented *Bacteroides* spp.	0.1 ± 0.1	0.3 ± 0.3	0.9 ± 0.8	1.4 ± 1.4
Lactobacillus spp.	1.1 ± 0.6	2.7 ± 2.3	0.3 ± 0.1	9.4 ± 5.3*
Staphylococcus spp.	0.0 ± 0.0	3.2 ± 1.9*	0.0 ± 0.0	3.5 ± 2.5*
Pseudomonas aeruginosa	0.3 ± 0.3	0.2 ± 0.2	0.3 ± 0.2	0.0 ± 0.0
Neisseria spp.	5.9 ± 3.3	12.0 ± 6.7	9.8 ± 4.6	17.2 ± 6.5
Streptococcus mutans	1.0 ± 0.7	2.2 ± 1.6	0.6 ± 0.5	0.1 ± 0.1
Veillonella spp.	19.9 ± 4.0	15.5 ± 6.6	21.1 ± 5.6	23.2 ± 6.8
Total yeasts	0.4 ± 0.4	0.5 ± 0.3	0.1 ± 0.0	0.6 ± 0.4*

[a] From Reynolds et al. (*65*).

[b] Values reported are the mean ± SEM ($n = 21$). Asterisks indicate a value of $P \leq .10$ for prechemotherapy and midchemotherapy differences (one-way analysis of covariance with repeated measures, controlling for differences related to antibiotic administration and hygiene protocol). Pretreatment total viable-cell count of *Staphylococcus* spp. was 0.002 ± 0.002.

Table 9. Microorganisms associated with acute periodontal infection in 13 acute leukemia patients[a]

Organism	Recovered only at acutely infected sites		Recovered at acutely infected and noninfected sites		
				Mean % of total microorganisms recovered ± SD	
	No. of infections	Mean % of total microorganisms recovered ± SD	No. of infections	Infected site	Noninfected sites
Pathogens					
S. epidermidis	0		5	35.2 ± 43.9	25.6 ± 21.7
Candida spp.	3	7.2 ± 11.1	4	36.7 ± 54.1	37.3 ± 44.2
P. aeruginosa and other *Pseudomonas* spp.	2	1.1 ± 1.3	0		
Other GNB	2	3.2 ± 4.0	2	4.5 ± 0.7	5.3 ± 6.7
Indigenous oral bacteria					
Veillonella spp.	1	89.5	1	40.0	40.0
Streptococcus mutans	0		1	30.0	31.0
Black-pigmented *Bacteroides* spp.	0		1	30.0	30.0

[a]From Peterson et al. (*54*). Total colony-forming units were determined on nonselective anaerobic blood agar.

cally suppressed; this observation is consistent with presentation of acute infection at nonoral sites during granulocytopenia (*66,67*).

For this study, subgingival specimens were collected under anaerobic conditions. This approach differs from techniques typically used to diagnose oral infections in these patients (*60*). Diagnostic culturing techniques commonly used for hospitalized patients (i.e., sampling of the attached gingiva with a sterile cotton-tipped applicator, as discussed above) may not precisely sample the acutely infected ulcerative site. The acute periodontal infections are not equivalent to mucositis, which results from the direct, stomatotoxic effects of cytotoxic drugs, with superinfection playing a secondary role; the periodontal infections should be viewed as an indirect result of reduction in host defenses occurring in a setting of chronic, preexistent periodontal disease. Thus, sampling the mucosa or attached gingiva may lead to inaccurate findings when only the periodontium is acutely infected.

These microbiologic findings collectively emphasize the importance of the periodontium as a nidus for infection in neutropenic patients. Such infection may be associated with either pathogens or increased numbers of indigenous oral bacteria. In addition to our studies, several other investigators have analyzed the dentition and periodontium as sources for acute, systemic infections in cancer patients (table 11). Lindquist et al. (*8*) evaluated 17 breast carcinoma patients receiving chemotherapy and related dental plaque levels to incidence and duration of "stomatitis" during granulocytopenia. The patients with no measurable dental plaque developed less severe stomatitis for a shorter duration; however, no statistical analyses for significance were presented. Greenberg et al. (*68*) reported that the oral cavity (most frequently the periodontium) was the likely source for seven of 12 episodes of septicemia in 33 ANLL patients; the authors concluded that potential oral sources of bacteremia should be eliminated prior to chemotherapy for acute leukemia. Hickey et al. (*13*) reported that prechemotherapy dental treatment, including dental scaling and oral hygiene instructions, resulted in less severe stomatitis in a

Table 10. Microorganisms associated with acute periodontal infection in 11 solid-tumor patients[a]

Organism	Recovered only at acutely infected sites		Recovered at acutely infected and noninfected sites		
				Mean % of total microorganisms recovered ± SD	
	No. of infections	Mean % of total microorganisms recovered ± SD	No. of infections	Infected site	Noninfected sites
Pathogens					
S. epidermidis	0		0		
Candida spp.	2	2.1 ± 2.8	1	0.5	0.2
P. aeruginosa and other *Pseudomonas* spp.	0		1	0.1	0.1
Other GNB	0		0		
Indigenous oral bacteria					
Veillonella spp.	3	64.9 ± 29.2	2	70.0 ± 28.3	40.0 ± 0.0
Streptococcus mutans	3	44.3 ± 14.0	3	80.0	41.7 ± 7.6[b]
Black-pigmented *Bacteroides* spp.	2	59.0 ± 36.8	0		

[a]From Peterson et al. (*54*). Total colony-forming units were determined on nonselective anaerobic blood agar.
[b]Isolate appeared at infected site in one patient and at noninfected sites in three patients.

Table 11. Reduction in incidence or severity of dental and periodontal infection

Authors (ref. No.)	Patient population (No.)	Intervention
Lindquist et al. (*8*)	Breast carcinoma (17)	Dental plaque evaluations
Beck (*9*)	Chemotherapy (47)	Toothbrushing, Cepacol mouthwash, Vaseline
Daeffler (*11*)	Cancer patients (NA)[a]	Survey and literature review
Greenberg et al. (*68*)	Acute nonlymphocytic leukemia[b] (33)	Prechemotherapy dental treatment
Hickey et al. (*13*)	Testicular carcinoma (21)	Prechemotherapy dental treatment ± water lavage
Wright et al.[c] (*69*)	Cancer patients (> 2,950)	Oral disease prevention program

[a] NA = Not available.
[b] Nine patients on initial study, 24 patients on modified study.
[c] Noncontrolled clinical trial.

study of 21 testicular carcinoma patients; however, the statistical analyses did not include levels of significance for differences between patients who received prechemotherapy dental care and those who did not. Wright et al. (*69*) summarized their experience with an oral disease prevention program in more than 2,950 cancer patients receiving radiation or chemotherapy; they concluded that a variety of potential oral sequelae associated with cancer therapy can be prevented, reduced in severity, or alleviated. The approach of thorough prechemotherapy periodontal assessment and therapy is qualitatively different than removal of all teeth in leukemic patients in remission (*70*); this philosophy is no longer advocated.

The design of these and other studies is based in part on a rationale for thorough dental scaling prior to remission induction. This rationale includes the following concepts: (*a*) dental scaling would lead to a reduction in factors that contribute to bacterial colonization; (*b*) healing of chronically infected periodontal tissues would be enhanced; (*c*) there would be reduced risk for acute exacerbations of chronic, preexistent periodontal infection; and (*d*) the incidence of fevers of unknown origin would be reduced.

Data from an unpublished trial at the University of Maryland Cancer Center are relevant to this rationale. Thirty-three newly diagnosed ANLL patients were randomized to receive either limited or thorough mechanical oral hygiene care prior to remission induction (table 12). Patients in the latter group who had $\leq$2,000 granulocytes/mm^3 received prophylactic broad-spectrum antibiotics 1 hour prior to the oral procedure and 6 hours after the initial dose. Limited-hygiene patients, who did not receive a thorough dental scaling prior to chemotherapy, experienced five acute, systemic infections clinically documented to be of periodontal origin; only one such acute, systemic infection was detected in a patient who received a thorough dental scaling prior to chemotherapy. There was no difference in the frequency of nonperiodontal infections between the two groups. The trend suggests that thorough dental scaling prior to chemotherapy would be of benefit in reducing subsequent risk of acute periodontal infection during granulocytopenia.

Our group (*71*) also recently analyzed the impact of a noninvasive oral examination versus invasive oral interventions (periodontal probing, dental scaling) prior to chemotherapy on subsequent development of fever and bacteremia in granulocytopenic cancer patients. Medical and dental records were reviewed for 100 patients who had been assigned to receive either the invasive or noninvasive procedure. Temperatures immediately before and up to 48 hours after the oral intervention were recorded, and occurrence of fever and bacteremia was documented for each group. There was no statistically significant difference in incidence of fever or bacteremia between the two groups of patients. Although periodontal probing and dental scaling invade mucosal barriers, such interventions did not appear to significantly affect the incidence of fever or bacteremia among the persons in this study.

SALIVARY GLANDS

There has been limited systematic investigation of salivary gland dysfunction in chemotherapy patients. If the nature and outcome of alterations in salivary gland function are understood, prophylactic approaches to restoration or replacement of the otherwise-compromised salivary function may become possible in the future. Most studies have investigated salivary gland abnormalities in patients receiving upper-mantle radiation or BMT (*72–74*). Conditions such as mouth breathing and oxygen support can have a dessicating effect on the oral mucosa; dysphagia can lead to pooling of oral secretions. These conditions, as well as true salivary gland dysfunction, could be expected to have a profound effect on patterns of both microbial colonization and oral disease.

Table 12. Oral and nonoral infection in ANLL patients[a]

Patient group	No. of patients	No. of infections (% of total)				
		Total	Acute periodontal[b]	Acute oral nonperiodontal	Acute esophageal, pulmonary, pharyngeal	Other
Limited oral hygiene	18	23	5 (22)	4 (18)	7 (30)	7 (30)
Thorough oral hygiene	15	22	1 (5)	4 (18)	9 (41)	8 (36)

[a] From Peterson et al., unpublished data. No diabetes or asymptomatic gingival infiltrate was present in any patient at admission.
[b] One episode per patient.

In 1981, Lockhart and Sonis (*7*) reported that chemotherapy induced minor salivary gland ductal dilation and acinar degeneration in 50% of patients reviewed at autopsy. Main et al. (*75*) described decreased salivary flow, reduction in salivary amylase and IgA levels, and a concomitant increase in levels of opportunistic pathogens in chemotherapy patients. These findings contrast with those of Schum et al. (*76*), who, in 1979, showed no significant changes in salivary flow rate, pH, or protein content in chemotherapy patients. Baum et al. (*77*) similarly found no change in flow rate or potassium levels, but observed significant reductions in sodium and protein levels in parotid and submandibular-sublingual gland secretions. As discussed by Schubert and Izutsu (*74*), comparison of findings among these various studies is difficult, since different study designs and cytotoxic drugs were used by the investigators.

SUMMARY

Future investigations of prechemotherapy strategies to prevent infection are needed. Priority should be placed on development of an internationally accepted classification system for the various stages of oral mucositis. Replication of trials of topical and systemic prophylaxis approaches as discussed in this review could then become more meaningful. In addition, there are sufficient data to warrant comprehensive study of the relation of compositional and quantitative salivary changes to the oropharyngeal microbial ecology prior to and during chemotherapy.

Second priority should be placed on the study of prechemotherapy prevention of periodontal and dental pulpal infections. It is necessary to clarify the relation of microbial dental plaque levels to subsequent occurrence and severity of oral mucositis, as well as types of organisms associated with acute pulpal infection in the neutropenic patient.

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Infection Prevention in Bone Marrow Transplantation and Radiation Patients

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This article reviews the prevention of oral and systemic infection in bone marrow transplantation and radiation patients. Prophylaxis of herpes virus reactivation in bone marrow transplant and leukemic patients has resulted in reduced morbidity associated with their medical management. In order to reduce the risk of systemic infection, reduction in ulcerative mucositis is desirable. The use of antifungal and antibacterial agents has not been encouraging to date. Cytoprotective agents have shown some initial success in preventing mucosal breakdown. Further study is required to confirm these initial results. [NCI Monogr 9:73–85, 1990]

There is considerable evidence that the oral flora may be the source of systemic infection in neutropenic patients (*1–13*). The oral flora may cause regional or systemic infection due to exacerbation of preexisting sites of infection, after acquisition of new pathogens, after reactivation of latent infection, or when access through oral ulceration occurs. Invasion through the mucosa may also occur.

Oral mucositis may provide a potential portal for infection. The pathogenesis of oral mucositis in cancer patients is related to the relative rate of epithelial cell turnover in the oral mucosa, degenerative changes in submucosal tissue, and vascular changes in the submucosa (*14–16*). Keratinized mucosa may be more resistant than nonkeratinized mucosa. Indirect effects on the oral mucosa that may influence mucositis include myelosuppression, local irritation, and microbial irritation (*14,17–20*). Reactivation of latent virus may directly affect the epithelium. Local irritation may be enhanced by reduction in saliva volume and changes in its consistency and constituents. By understanding the etiologic factors, advances in prevention and treatment can be anticipated.

MANAGEMENT OF PRETREATMENT CONDITIONS

Acute symptomatic infection must be managed prior to myelosuppressive therapy and radiotherapy that will include the area in the treatment volume. Chronic infection without symptoms may not be exacerbated during neutropenia, although removal of all potential foci of infection should be completed if possible (*20,21*). Dental and periodontal sources of infection must be examined thoroughly. Local irritants, such as calculus on the teeth or prostheses, should be reduced, and rough irregular surfaces due to cavities, broken teeth or restorations, and prostheses should be smoothed and polished. As denture surfaces may be colonized with *Candida* species, attention to denture hygiene and removal of the appliance at least at night is recommended. When the denture is not in the mouth, it should be soaked in an antiseptic solution, as denture cups containing water have been shown to be colonized with a variety of pathogens (*22*).

SUPPRESSION OF COLONIZING ORGANISMS

Potential oral sources of infection include chronic dental or periodontal conditions and periodontal and mucosal colonization. Septicemia due to oral sources has been estimated to occur in from 25% to over 50% of immunosuppressed patients (*5,7,12*). Dreizen and colleagues (*1,2*) have described bacterial infections of the oral cavity in approximately one-third of patients with acute leukemia. Up to 50% of all oral infections in patients with acute leukemia have been reported to be of fungal etiology, primarily *Candida* species (*2,17,23*).

Good oral hygiene reduces the quantity of oral flora, albeit temporarily. It has been suggested that good oral hygiene may reduce the development and severity of oral mucositis that may occur during therapy (*12,24–29*). Therefore, oral hygiene instruction is thought to be important and patients should continue with thorough dental hygiene before, during, and after medical therapy. However, there are no controlled studies of large numbers of patients in whom oral hygiene has been shown to be effective in reducing oral and systemic complications. Greenberg and co-workers (*12*) reported an oral source of septicemia in 25% of patients with acute leukemia who received dental care and scaling prior to chemotherapy, compared with 77% of patients who did not receive dental care prior to chemotherapy. The infection most likely to be exacerbated is preexisting periodontal disease (*8,30*). Acute exacerbation of periodontal lesions was studied in 27 episodes in 24 patients (*30*). A single pathogen was identified in 10 cases, and more than one organism was recovered in seven cases. *Staphylococcus epidermidis, Candida albicans, Staphylococcus aureus,* and *Pseudomonas aeruginosa* predominated. They found that pathogens associated with infection in myelosuppressed cancer patients as well as the indigenous flora may be identified in periodontal infection. Asymptomatic periapical pathosis does not appear to be exacerbated in immunosuppressed patients, possibly due to the broad-spectrum antibiotics administered to these patients (*20*).

Saline rinses have been recommended to help reduce mucosal irritation, remove thickened secretions and debris from the mouth, and increase moisture in the mouth. It has also been recommended that sodium bicarbonate may increase the alkalinity of the rinse for a patient who is vomiting. Hydrogen peroxide rinses have also been suggested (*27,28*). However,

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this type of rinse may be irritating to the tissue, and patient compliance is limited. Hydrogen peroxide may assist in removing clots and debris and may be of value in periodontal infection when anaerobic organisms are involved. In spite of these recommendations, no clinical studies on the efficacy of these rinses could be found in the literature.

Oropharyngeal Candidiasis

Leukemia and Bone Marrow Transplant Medicines

Oropharyngeal candidiasis (OPC) may extend regionally and cause fungemia that may result in death in immunocompromised cancer patients (*31–42*). Systemic candidiasis (SC) may be the immediate cause of death in at least one-third of immunocompromised cancer patients (*43*). The death rate for neutropenic patients who develop disseminated candidiasis has been estimated at 72%–88% (*44–46*). Almost all cases of SC were documented to follow colonization of the oral cavity or occurred in patients who had preexisting OPC (*47*). Schwartz et al. (*41*) reviewed 54 consecutive admissions for 67 courses of remission induction chemotherapy; invasive fungal disease was seen in 22% of the subjects, with a mortality rate of 60%. Among patients who underwent autopsy, disseminated fungal infections were reported in 22%–56%; premorbid diagnosis was made in from 0% to a maximum of 28% of these cases (*37,39,45,48*). Risk factors include duration of chemotherapy, severity and duration of neutropenia, and number of sites colonized by fungi. Prevention of colonization of the oropharynx and prevention of clinical OPC may be of critical importance in prevention of SC.

Studies on the ability of topical oral antifungal preparations to reduce colonization have shown conflicting results. Topical antifungal agents, including polyenes, and topical and systemic imidazoles have been studied in prophylaxis, but each is limited in efficacy or by toxicity (*31,33–35,47,49–58*).

Polyene antibiotics. Carpentieri and co-workers (*55*) reviewed attempted prophylaxis of *Candida* infection in 94 children with leukemia. They found that colonization was not reduced in patients given nystatin prophylaxis, but fewer cases of clinical candidiasis were seen. In another study of patients with acute leukemia, nystatin prophylaxis was compared with natamycin and no prophylaxis (*52*). In this study, all patients were given hexetidine 0.1% rinse. No detailed oral assessment was made, but there was no evidence of differences among the three groups. This may be in part related to the routine use of hexetidine, but a lack of additional effect of nystatin was reported. A study of antibiotics and nystatin for suppression of alimentary tract organisms did not reduce the number of carriers of *Candida* species and did not reduce new colonization by *Candida* species (*49*). De Gregorio et al. (*47*) followed 93 admissions of 70 patients undergoing chemotherapy for acute leukemia. In 55 admissions, the patients received nystatin rinse; the rinse was not used for the other admissions. Nystatin prophylaxis was not randomized but was used at the discretion of the attending physician. For age, sex, type of leukemia, chemotherapy, severity and duration of leukopenia, and use of antibiotics, treatment outcome was not different between the groups. The patients who developed OPC were more severely leukopenic (<500 cells/mL), had an extended duration of leukopenia, and received more antibiotics. Approximately 60% of patients in both groups developed OPC. De Gregorio et al. (*47*) identified 13 cases of systemic *Candida* infection, and all but one case had previously diagnosed OPC. Prophylactic use of nystatin did not affect clinical OPC or SC. Despite nystatin rinse prophylaxis, approximately 30% of leukemic patients in three studies developed clinically diagnosed OPC (*17,50,59*). Barrett (*50*) reported follow-up of 33 patients who developed neutropenia. He evaluated only those patients who appeared to comply with nystatin-rinsing regimen (1 mL four times daily for 1 min). Patients were evaluated daily. Even when data for noncompliant patients were eliminated, he could not show that colonization by *Candida* spp. was affected. A major problem in the use of nystatin is limited compliance due to nausea, vomiting, and complaints of taste (*60*). Aviles (*61*) reported a clinical review of oral nystatin prophylaxis. The nystatin group consisted of 284 patients, of whom 1.7% developed candidiasis. In the placebo group of 170 patients, 32% developed candidiasis. Aviles (*61*) also reviewed their clinical experience and found that the incidence of lethal candidiasis in those using nystatin was reduced from 28 cases among 186 patients between 1967 and 1970 to three cases among 58 patients between 1971 and 1984. This appears to be the most optimistic report on the use of a nystatin rinse in immunocompromised patients.

Imidazole agents. Brinkner (*56*) studied an oral preparation of miconazole in patients with leukemia or lymphoma and found an effect on clinical infection in cancer patients. Schechtman and others (*62*) conducted a double-blind study with clotrimazole troche in treating oral candidiasis in 13 patients with acute leukemia or lymphoma. The oral cavity was examined for adherent plaques, and diagnosis was made by the presence of pseudohyphae in mucosal scrapings. Among the patients receiving clotrimazole, *Candida* esophagitis developed in one of seven; in the placebo group, five of six patients required treatment with amphotericin B for progressive candidiasis. No toxicity was reported.

A randomized trial to compare the oral use of a clotrimazole troche and nystatin vaginal tablet used five times daily was conducted in cancer patients (*63*). The patients represented a wide range of cancers, and thus the medical therapy was quite varied in drug type and intensity of therapy. Lawson and Bodey (*63*) found that both treatments appeared to reduce clinical candidiasis, as determined by global clinical assessment and microbiology. Nystatin was associated with more frequent nausea and thus with poorer patient acceptance.

Ketoconazole has been assessed in studies in bone marrow transplant (BMT) and leukemia patients (*54,59,64*). Similar results were seen with the use of ketoconazole and miconazole, with surveillance cultures, OPC, and SC being similar in both groups (*54*). In non-BMT subjects, prophylaxis with ketoconazole was superior to that with amphotericin B and nystatin (*59*). Serum levels of ketoconazole fall in BMT patients owing to impaired absorption from the gastrointestinal tract, which was associated with reduced evidence of prophylactic effect (*59*). The requirement for food intake and the role of stomach acidity in absorption of oral ketoconazole are well known (*54,59*). Ketoconazole was found to be effective in reducing the number of positive sites found by surveillance cultures. Malcom et al. (*64*) reported the use of ketoconazole in prevention of OPC in neutropenic patients. They conducted a randomized study of ketoconazole and nystatin in patients with <1,500 neutrophils/mL. Daily oral examinations and weekly surveillance cultures were performed. Of the 10 patients in the ketoconazole group,

oral candidiasis occurred in two and *Candida* esophagitis in one; of the 11 patients in the nystatin group, four developed OPC and two developed SC. Ketoconazole may be useful in prophylaxis, but liver toxicity and limited absorption are problems.

Topical antifungal agents used in combination may have greater potency and may reduce or prevent colonization or reduce the development of disease or dissemination (*59*).

Chlorhexidine. Topical antiseptic rinses with chlorhexidine have shown encouraging results in studies with cancer patients (*56,65–70*). Langslet and others (*65*) first reported the use of chlorhexidine in the topical treatment of pseudomembranous candidiasis in seriously diseased children. In their report, five of eight patients with candidiasis had a diagnosis of leukemia. They reported improvement in the clinical condition of these patients and suggested that prophylactic use of chlorhexidine rinses may be indicated. Shepherd (*71*), in a study of leukemic patients, found that 0.2% chlorhexidine reduced the total number of oral microorganisms by 98% immediately after rinsing. The majority of organisms were gram-positive anaerobes. Spiers et al.(*66*) reported that rinsing with chlorhexidine every 2 to 3 hours eliminated bacteria and yeasts in patients with acute leukemia during neutropenia. During this protocol of intensive topical chlorhexidine rinsing and systemic preventive therapy, no patients developed systemic infection during intensive chemotherapy (*66*). However, this report was not double blind in nature. Retention of chlorhexidine in the oral environment after use of an oral rinse and a chlorhexidine gel has been studied (*72*). Multiple mouth rinses with chlorhexidine led to accumulated retention, with 0.2% rinse showing greater retention than less concentrated rinses. Retention of the drug in the oral cavity may be of importance in the clinical effect of chlorhexidine.

McGaw and Belch (*67*) studied the prophylactic use of chlorhexidine 0.1% rinse twice daily in 16 patients with acute leukemia in a treatment and a placebo group. They found improvement in gingival health, plaque scores, and mucositis in the chlorhexidine group. Patients were followed for a 4-week period. They also found that half of the placebo group developed clinical candidiasis and that none of the chlorhexidine group did. A trend to fewer febrile days was seen in the chlorhexidine group. They believed that the reduction in complications in patients using the chlorhexidine rinse reflected a reduction in the oral flora. Compliance with the oral rinses was reported as excellent, but no estimate of the frequency of use or duration of rinsing was given. This study represents encouraging results for a small number of cases.

Ferretti and others (*68–70*) have published several reports on the use of chlorhexidine rinse (0.12%) in patients receiving bone marrow transplantation (BMT). The first report by this group (*68*) presents four cases. These patients were part of their controlled study who were removed from study due to oral complications during BMT and were found to be on the placebo arm. These four patients were then given chlorhexidine rinse. They comment that the antifungal effect of chlorhexidine was dramatic and state that amphotericin B did not resolve candidemia until the chlorhexidine rinse was added. The implication is that resolution was directly related to chlorhexidine. However, this cannot be verified, as the systemic state of the host was not described, and this may represent the common course of healing of mucositis. However, this report was only an extract of their study. Their study was also reported in two articles (*69,70*). Their study consisted of clinical examinations by one investigator. The rinses were delivered by the nursing staff, which may have led to inconsistencies in their use. All patients were treated in similar fashion with prophylactic antibiotics, acyclovir, and nystatin oral suspension, and clotrimazole troches were given when patients were unable to swallow nystatin without emesis. Empiric amphotericin B was added if patients remained febrile for 48–72 hours in spite of broad-spectrum antibiotics. In their earlier report (*69*), 33 patients were evaluated. In their more recent report (*70*), 51 BMT patients were evaluated. The results presented do not allow the number of patients at each visit to be assessed in a clear manner, but patient dropout did occur, reducing the number available for evaluation at the final visits. Part of the trial extended for some patients both in and out of the hospital for a total of 60 days of rinsing. They reported a statistically significant reduction in the number of patients with mucositis and significant reduction in severity of mucositis in the chlorhexidine group. For the placebo group they reported ongoing mucositis at days 33 and 90 in approximately 40% of the patients, a surprisingly large number for toxicity due to chemoradiotherapy, and probably the result of protracted hematologic recovery being different between the two groups or other causes, such as graft-versus-host disease (GVHD) or other infection. During hospitalization, statistically significant differences were reported at day 7, day 25, and day 33 in frequency of mucositis and severity of mucositis. However, when the most severe reaction was compared, no statistically significant difference was seen (day 14). The duration of mucositis was apparently less in the chlorhexidine group, but evaluation of these findings should be made with a review of hematologic status, together with the finding that oral hygiene levels were consistently poorer in the control group. They reported significant reductions in the number of streptococci, which were significantly different between groups at days 14, 25, 33, and 60. No significant differences were seen in the presence of gram-negative (aerobic) organisms, and no differences were seen in the number of positive blood, urine, and throat cultures during the study. They did report significant differences in candidiasis at days 14, 25, and 33. They also reported *Candida* sepsis in 19%, positive blood cultures in 29%, and *Candida*-related deaths in 4% of the patients in the placebo group, whereas they did not identify any of these events in patients rinsing with chlorhexidine. The use of amphotericin B was not different between groups. This finding suggests that there were no identified differences between those on chlorhexidine or placebo rinse in fever not responding to broad-spectrum antibiotics or identification of SC. They also reported that fewer patients in the chlorhexidine group required morphine and that they required it for fewer days.

Data have been presented to suggest that chlorhexidine has antiviral activity (*73*). Inhibition of the replication and cytotoxic effect of herpes simplex virus (HSV) in cell culture was shown. In a murine model, chlorhexidine moderately reduced the development of viral lesions and reduced viral titers in the trigeminal ganglia. These findings are of interest and suggest the need for further study. However, the study by Weisdorf et al. (*74*) did not demonstrate that rinsing with chlorhexidine reduced the incidence or duration of oral HSV infection in patients undergoing BMT.

Sharon and others (*75*) reported on the effect of chlorhexidine rinses on candidiasis in patients with leukemia. They studied 18

patients with leukemia, 15 of whom carried *Candida* species. Cultures were performed on unstimulated whole saliva samples for *Candida* organisms. Nine of these subjects were placed on chlorhexidine, but no reduction in the number of colony-forming units of *Candida* organisms was seen. They believed that the lack of in vivo effect was due to rapid recolonization from oral sites not affected by the oral rinse.

Multiagent trials. Combinations of topical and systemic antifungal agents may have enhanced prophylactic and therapeutic effect. Berkowitz and others (*38*) reported a study of 16 consecutive pediatric patients receiving BMT with whom a multiagent regimen for antifungal prophylaxis was studied. The regimen consisted of debriding mucosal surfaces with povidone-iodine swabs four times daily, swabbing all mucosal surfaces with a cotton pledget soaked with 500,000 units of nystatin, and oral ketoconazole once daily. This protocol was continued until the neutrophil count was >500/mL. Oropharyngeal mucositis developed within 4–6 days posttransplant at the wbc count nadir. Resolution occurred in 16–27 days posttransplant, when the neutrophil count was approximately 500/mL. Fifty percent of the patients did not carry *Candida* organisms at admission and remained noncolonized during treatment. Among the 50% who had a positive baseline culture, follow-up cultures were negative for most, and three patients had sporadically positive cultures. Berkowitz et al. reassessed their previous experience and noted that the majority of patients did not swish adequately. They also believed that the presence of necrotic debris and extensive plaques on the mucosa may have limited the effectiveness of rinsing in this pediatric group. This multiagent protocol was reported to reduce the organism counts below the threshold of detection. Thirteen of 16 patients did not develop clinical OPC. None of the patients developed *Candida* esophagitis or systemic infection during neutropenia. Further double-blind protocols and evaluation of multiagent prophylaxis appear to be warranted.

Kostiala and others (*76*) compared the effect of clotrimazole and chlorhexidine in topical treatment of clinical fungal stomatitis in patients with hematological malignancies. A total of 85 episodes of candidiasis were studied in 53 patients. Clotrimazole tablets were compared with chlorhexidine rinse, both used five times daily. Of 96 episodes of *Candida* stomatitis, 11 were excluded for such problems as lack of compliance, incomplete follow-up, and death due to systemic disease. Approximately half of the episodes were treated with each agent, with a cross-over design if no improvement was seen after 5 days. Swab and expectorated saliva specimens were collected. The majority of patients were neutropenic. Kostiala et al. reported a statistically significant reduction in clinical candidiasis in the clotrimazole group. Of the clinical infections, clinical cure was noted in 60% of the clotrimazole and 29% of the chlorhexidine rinse groups ($P < .01$). Systemic antifungal agents were administered to more of the clotrimazole subjects. However, six of the 11 patients in the clotrimazole group responded well to systemic agents, whereas none of the chlorhexidine group responded well.

Spiers et al. (*66*) used an intensive regimen of topical chlorhexidine rinses, brushing with chlorhexidine, and nystatin rinses and found that the oropharynx was difficult to decontaminate, as no growth on culture of the oral cavity was found for only two of 18 subjects.

Weisdorf and others (*74*) recently published a prospective double-blind trial of chlorhexidine in oral mucositis for BMT patients. One hundred patients were randomized to the study and followed up until day 35 post-marrow transplant. Of these, 89% were evaluated for the duration of the study. Routine oral hygiene consisted of brushing twice daily and rinsing with salt-soda rinses. All patients were provided clotrimazole troches or nystatin rinse. They rinsed with either drug (0.12% chlorhexidine) or placebo three times daily. There was 71.8% ± 24.5% compliance with the chlorhexidine rinse and 77.4% ± 18.8% compliance in the placebo group. Weisdorf et al. assessed mucositis twice weekly by measuring the area of ulcerated oral mucosa at seven oral sites, and a mean ulceration score was developed. Pain was scored on a four-point scale. They could not demonstrate an effect of the chlorhexidine in reducing mucositis. Maximum ulceration in the chlorhexidine group was 18% ± 22% of the oral mucosa, and in the placebo group it was 25% ± 31%. They could not demonstrate any therapeutic advantage of chlorhexidine in reducing mucositis, oral pain, oral infection with HSV, or hospital stay. They identified a trend to reduced dental plaque ($P = .06$) and less frequent candidiasis ($P = .06$), and perhaps candidemia, in chlorhexidine users. There was no evidence of reduction in bacteremia, even that due to alpha-hemolytic streptococci. Patients who received methotrexate for GVHD prophylaxis were at higher risk of oral mucositis, and mucositis was worse in adults.

Study at Vancouver General Hospital

My colleagues and I conducted a clinical study of patients admitted to the Leukemia/Bone Marrow Transplant service of the Vancouver General Hospital, Vancouver, BC, Canada. Patients were assigned by their primary nurse to one of four groups at admission in a sequential manner. Patients were provided with an oral rinse four times daily. The rinse groups were chlorhexidine alone, nystatin alone, nystatin and chlorhexidine, or saline. The rinses were provided by the nursing ward staff. All patients received medical therapy that resulted in severe neutropenia. Of the patients, 65% received aggressive chemotherapy for remission induction or consolidation and 35% received BMT, with a conditioning regimen that included radiation for 63.3% of all BMT patients in the trial.

Patients were evaluated when they had been in the hospital a minimum of 3 weeks. All patients included in the analysis developed severe neutropenia (<100 neutrophils/mL) during the study period. With these criteria, 86 patients were included in the analysis. There were 53 males and 33 females, with a mean age of 40.3 ± 16.5 years. The medical diagnoses are shown in table 1. They were assigned to rinse groups as shown in table 2. There were no statistical differences in age, sex, medical diagnosis, or medical therapy between rinse groups. Compliance with use of the oral rinses during hospitalization was assessed. Those who were assigned to rinse with nystatin either alone or with chlorhexidine were less compliant, with 53% in the nystatin-chlorhexidine rinse group using the rinse less than 100% (i.e., four times per day). Among those using chlorhexidine, 78% used the rinse every time it was provided, and the saline group complied at all times in 89% of the cases ($P = .005$).

During medical management, 62.8% of the patients developed temperatures of >38 °C, and 31.4% of the patients had a

Table 1. Patient population

Diagnosis	No. (%) of patients
Aplastic anemia	3 (3.5)
Acute myelocytic leukemia	47 (54.7)
Acute nonlymphocytic leukemia	3 (3.5)
Acute lymphocytic leukemia	18 (20.9)
Chronic myelogenous leukemia	9 (10.5)
Granulocytic sarcoma	3 (3.5)
Other	3 (3.5)

temperature of >38 °C at the time of the maximum mucositis score.

There were no differences in colonization noted prior to entry between the groups. Of the 86 patients, 62 had normal cultures of oral flora and 15 (18.8%) were colonized with *Candida* spp. prior to treatment; 7.1% of the patients harbored organisms not indigenous to the oral cavity, including *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp., and others. During therapy, 30% of patients were identified as *Candida* positive and 25% of patients demonstrated nonindigenous bacterial flora. During treatment, 26% of patients developed positive blood cultures. Only five patients (5.9%) developed bacteremia with oral organisms and positive blood culture for the same organism. There were no significant differences in the presence of *Candida* species or nonindigenous flora between rinse groups. No microbial growth was reported in 12.9% of patients, all of whom had been rinsing with chlorhexidine alone or combined with nystatin ($P = .0029$). This was the only statistically signficant result of this study. There were no differences noted between rinse groups in measures of ulceration or ulceration and erythema combined (table 3). We also did not detect any differences in plaque levels during treatment or differences in the gingival index. We also reviewed the findings by using log-transformed data and analysis of variance and could not identify any other statistically significant differences or trends.

Table 2. Rinse groups

Rinse group	No. (%) of patients	No. of patients by diagnosis		
		Acute	Chronic	Other
Nystatin + chlorhexidine	34 (39.5)	24	6	4
Nystatin	16 (18.6)	13	2	1
Chlorhexidine	18 (20.9)	16	1	1
Saline	18 (20.9)	15	3	0

Radiation Mucositis

Radiation mucositis may provide a more easily studied model of mucositis because of the predictable development of mucosal reactions when tumoridical radiotherapy is used and fewer confounding factors than in BMT. In BMT, confounding factors include use of antimicrobial agents, GVHD, and hematologic status.

In radiation therapy, the most common infection in the oropharynx is candidiasis (*77–80*). The number of patients with positive *Candida* cultures increased from 22% before radiation treatment to 49% at the end of therapy and to 59% in follow-up (*77*). Quantitative cultures of *Candida* spp. increased in approximately 30% of patients receiving radiation therapy (*79,80*).

The effects of chlorhexidine and benzydamine (BZD) were compared in a group of radiation patients (*81*). The 25 subjects in this study were undergoing radiotherapy following surgical management for oral cancer. They were assigned to either the BZD or chlorhexidine rinse group, rinsing twice daily. Mucositis was graded on a global scale as none, mild, moderate, or severe. Microbiologic studies included *Candida*, coliform counts, and *Staphylococcus aureus*. Of the 25 patients, 23 harbored *Candida* or coliforms on one or more occasions during the study. No significant differences were seen in mucositis rating, pain, or *Candida* and coliform carriage. They found that neither rinse provided a therapeutic advantage. They identified limited compliance with the BZD rinse because it caused a burning sensation. Their study was not double-blind because of the different rinses used. They concluded that few data exist on the efficacy of oral topical agents against the development of oral mucositis.

Chlorhexidine rinse has been studied in the prevention of irradiation mucositis (*82*). Thirty patients were enrolled in a double-blind trial with a 0.1% chlorhexidine rinse. There were no differences in age, sex, tumor staging, or dose of radiation between groups. Radiation was administered at 2 cGy daily for 25 fractions. Subjects were followed for 5 weeks. Twenty percent of the patients in both groups were colonized with *Candida* organisms prior to radiotherapy. During treatment, two cases of clinical candidiasis were seen in the placebo group, and none were seen in the chlorhexidine group. No differences were seen in *Enterobacter*, *Pseudomonas*, and *Actinobacter* species. No differences in the development or severity of mucositis were seen. Changes were reported only for the gram-positive aerobic flora, with a reduction in the number of streptococci in the chlorhexidine group.

Table 3. Assessment of oral mucositis during treatment

Rinse group	Ulceration score				Mucositis score			
	Average		Maximum		Average		Maximum	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Nystatin + chlorhexidine	7.59	22.67	24.68	56.45	3.01	1.74	3.95	1.84
Nystatin	4.06	30.16	13.13	38.06	2.95	1.49	3.45	2.11
Chlorhexidine	8.11	19.54	20.56	34.31	2.61	1.63	3.53	1.89
Saline	5.94	10.90	16.00	31.07	2.05	1.88	2.46	2.28

SUPPRESSION OF REACTIVATING ORGANISMS

Dreizen et al. (*83*) reviewed the records of 1,263 patients with leukemia and found herpetic infections in 25% of these patients. A patient who is seropositive for HSV has a 50%–80% chance of reactivation of viral infection during chemotherapy or BMT (*17,84–93*). These infections in immunocompromised patients are severe and associated with morbidity, and the associated ulceration may occur at sites of potential secondary bacterial and fungal infection. In a study of patients receiving allogeneic BMT, 204 of 330 HSV-seropositive patients with IgG titers >1:8 developed HSV infection (*89*). Prophylaxis of infection has become routine for HSV-seropositive patients due to the frequency of reactivation (*84,93–95*).

Chronic low-dose (200 mg daily) acyclovir in nonimmunocompromised patients has been shown to be effective prophylaxis, and no resistant virus developed (*96–98*). For BMT patients in the first year posttransplant, those susceptible to HSV may be maintained on low-dose acyclovir according to the findings of a study on nonimmunocompromised patients. However, studies of low-dose prophylaxis in immunocompromised cancer patients are needed.

Breakthrough of acyclovir prophylaxis and development of clinical HSV infection are known, and resistant HSV isolates have been reported (*99–106*). In a study of 2,400 HSV isolates, 7%, primarily from immunocompromised patients, were resistant to acyclovir (*102*). In the immunocompromised patient, resistant HSV may produce clinical disease and become a management problem (*99,102,104,107*). These reports indicate the importance of prudent and appropriate use of acyclovir and other antiviral agents. Epstein and others (*108*) have suggested that use of acyclovir in patients with leukemia during aggressive medical therapy may be indicated for patients who are HSV seropositive, and when the lymphocyte count is less than 600/mL^3 and the monocyte count is less than 250/mL^3. In this manner, the risk-benefit ratio of the use of acyclovir can be maximized and the costs can be minimized.

CYTOPROTECTIVE APPROACHES

Prevention or reduction in mucositis may be achieved by pretreatment management of local irritants, reduction of colonizing organisms, prevention of reactivation of organisms (i.e., HSV), and management of xerostomia. In addition, initial studies of the prophylactic use of other agents that may reduce the development of mucositis suggest the need for further research.

Benzydamine Hydrochloride

Benzydamine (BZD) is a nonsteroidal drug that possesses analgesic, anesthetic, anti-inflammatory, and antimicrobial properties (*109–113*). BZD affects the chemical mediators of inflammation, including prostaglandin, serotonin, histamine, and acetylcholine (*109,111–116*). BZD has a stabilizing effect on cell membranes, inhibits degranulation of polymorphonuclear leukocytes, and inhibits platelet aggregation (*112, 115–118*). The common mechanism of action may be stabilization of cellular and intracellular membranes (*116*).

BZD administered systemically or topically has not been associated with major toxicity, and no allergic reactions have been reported (*118–121*). Topical application results in a concentration in mucosa greater than the minimal tissue concentration needed for local anti-inflammatory effect (*122*). The primary site of metabolism is the liver. The metabolites and free BZD are excreted in urine and in bile (*111,119,121,123*).

Mucositis in Chemotherapy

Sonis and others (*124*) reported a clinical trial of BZD rinse in the management of chemotherapy-induced mucositis. Palliation was reported in seven of nine patients. Their results indicated the need for a controlled clinical study. Schubert and Newton (*125*) reported a preliminary review of a double-blind study of BZD in the treatment of pain associated with mucositis in patients receiving BMT. It was suggested that prophylactic use may be more effective than therapeutic use.

Prevention of Mucositis in Radiation Therapy

Prada and others (*126,127*) conducted a study of BZD rinse versus bicarbonate rinse in patients receiving radiation and intra-arterial chemotherapy for head and neck cancer. Patients were followed for 10 days after treatment. BZD was reported to be more effective in controlling the symptoms and signs of mucositis. Statistically significant differences were reported for the symptoms of burning, oral pain, and odynophagia between the BZD and placebo groups. BZD was shown to delay the onset of mucositis and to significantly reduce edema and lysis of the epithelium. These findings indicated a histoprotective effect of BZD as a prophylactic rinse in cancer patients. Kim and co-workers (*128*) conducted a double-blind therapeutic clinical trial of BZD in radiation-induced mucositis. Patients were provided with the rinse at the time of onset of mucositis and were followed for 4 days. In this short-term trial, BZD significantly reduced mouth and throat pain and was associated with less-severe mucositis. Evidence of the anti-inflammatory action of the BZD rinse has been reported for radiation associated with oral mucositis (*126,128*).

Epstein and Stevenson-Moore (*129*) have shown that BZD was superior to placebo in reducing pain and in reducing analgesics needed during radiation therapy. The pain relief was without significant anesthesia, which is an advantage, as the risk of affecting the gag reflex and taste sensation and the risk of aspiration are reduced (*125,128–130*). The duration of pain relief was 0.5–2 hours with repeated doses needed to achieve maximum pain-relieving effect.

Lever et al. (*131*) reported on the use of BZD in several case studies in children. They initiated a non-blinded cross-over study in patients at risk for chemotherapy-induced mucositis. The rinse was used in cross-over fashion every 2 days with a combination rinse of nystatin and lidocaine in saline. The agents were administered by rinsing or by swab application. Only four patients completed the study. Among these subjects, pain relief was reported for 1 hour, but the BZD rinse caused a burning sensation that limited its use. This study was not double blind, and the rinses were evaluated on a schedule of only a few days, limiting the ability to thoroughly assess the agents studied. The design of this study led to its discontinuance.

Study of BZD in Prevention of Radiation Mucositis

A prospective, double-blind, placebo-controlled trial was completed among patients receiving radiation therapy to the oropharyngeal region for treatment of cancer at the Cancer

Control Agency of British Columbia, Vancouver, BC, Canada. Patients rinsed four times daily with BZD or an identical placebo rinse without BZD, before and during radiation therapy. They were assessed once weekly. The severity of mucositis was graded by the area of involvement, degree of inflammation, maximum size of ulceration, and total area of ulceration for each surface of the oral cavity involved. A total score for mucositis was developed by multiplying the degree of inflammation by the other variables in order that the total score be more representative of the severity of the tissue reaction. Pain was assessed by using visual analog scales.

Forty-nine patients were enrolled, with 43 completing the trial. Compliance was a greater problem in the placebo group, and six patients in the placebo group did not complete the study. Noncompliance appeared to be the result of lack of therapeutic effect of the placebo rinse. The experimental group included 25 patients, 14 men and 11 women, with a mean age of 63 years (range, 39–80 yr). The control group included 18 patients, nine men and nine women, with a mean age of 58 years (range, 26–76 yr). The medical diagnoses are shown in table 4. There were no statistically significant differences between the drug and placebo groups in age, sex, tumor stage, location, or type of radiation treatment.

Prevention of mucositis was seen in the BZD group compared to the placebo group (table 5). The total mucositis score was lower in the BZD group than in the placebo group ($P = .001$). The average area of mucositis during radiation therapy and the maximum mucositis score were significantly lower in the BZD group than in the placebo group ($P = .05$). The maximum size of ulceration and the total area of ulceration were less in the BZD group ($P = .04$ and $P = .05$, respectively). There were no differences between the two study groups in the development of secondary candidiasis during radiotherapy, with 12% of patients demonstrating clinical findings and cultures positive for *Candida albicans*.

All patients reported increasing oral discomfort during radiation therapy. Systemic medications were begun earlier during the course of radiotherapy in the placebo than in the BZD group. There were no statistically significant differences in the use of systemic analgesics, but a trend to less use of narcotic analgesics was seen in the BZD group. Approximately half of the patients in both groups began using a lidocaine rinse. However, one-third of the BZD group discontinued using lidocaine after the initial use, whereas all of the placebo group continued using the lidocaine rinse.

Table 4. Diagnoses of radiation-treated patients in BZD trial

Diagnosis	No. of patients	
	Benzydamine	Placebo
Squamous cell carcinoma		
Stage 1	2	1
Stage 2	9	5
Stage 3	5	5
Stage 4	7	2
Adenocarcinoma	1	2
Pleomorphic adenoma	1	1
Other	0	2
Total	25	18

Table 5. Oral mucosal breakdown in the BZD and placebo rinse groups

Measure	BZD group[a]	Placebo group[a]	*P* value (*t*-test)
Maximum size of ulcerations (cm^2)	0.73 ± 0.30	1.26 ± 0.40	0.04
Total area of ulcerations (cm^2)	1.61 ± 0.42	2.28 ± 0.52	0.05
Average area of mucositis (cm^2)	2.10 ± 0.36	2.68 ± 0.44	0.05
Area of reaction × severity of inflammation/surfaces involved	2.20 ± 0.56	3.29 ± 0.51	0.01

[a] Values are means ± SE. Calculations were made with log-transformed data.

Burning discomfort was associated with use of the study rinses when mucositis developed. None of the BZD group discontinued use of the rinse, and 15% used the rinse diluted with water when severe symptoms developed. However, 10% of the placebo group stopped use of the rinse, and 33% diluted the rinse in order to continue use. Fewer patients using BZD needed to dilute the rinse, and no patients stopped rinsing, suggesting that BZD reduces the sensation of burning associated with other components of the rinse.

BZD used as a prophylactic rinse as part of an oral care protocol was shown in this study to limit mucositis due to radiation therapy. The reduction in mucosal ulceration may reduce the risk of secondary infection. Resolution of mucositis following radiation therapy may be accelerated. If ulcerated mucositis can be prevented, one of the treatment-limiting toxic effects can be reduced. The findings of this trial have implications for the management of mucositis due to radiotherapy and for other causes of oral tissue breakdown, including chemotherapy, trauma, infection, and oral dermatoses.

Sucralfate

Sucralfate has also been suggested to be useful in the management of oral mucositis (*132–134*). Sucralfate is cytoprotective on gastric mucosa and will protect the mucosa from irritants (*135*). It may form a barrier at the site of ulceration and stimulate the synthesis and local release of prostaglandins (*136*). Ferraro and Mattern (*132,133*) reported four cases of chemotherapy-induced oral ulcerations that resolved within 48 hours following use of a sucralfate suspension. Adams and others (*134*) noted alleviation of pain and resolution of mucositis in five patients, two with radiation-induced and three with chemotherapy-induced mucositis.

Shenep and others (*137*) studied the use of an oral sucralfate suspension for chemotherapy-induced mucositis in a pediatric population. Forty-eight subjects with acute nonlymphocytic leukemia were studied in a double-blind protocol. Mucositis was monitored by using a global four-point scale, and pain was assessed on a five-point scale. Compliance was monitored by ward nursing staff. This trial was designed to detect changes of greater than 40%, and thus findings that were not reported as "significant" must be interpreted with this in mind. No signifi-

cant reduction in severity of mucositis was reported. Patients using sucralfate were less likely to become colonized with potentially pathogenic organisms than were those using placebo ($P = .008$). Fifty-eight percent of the sucralfate users reported less oral pain, compared to 25% of placebo users ($P = .06$). They reasoned that sucralfate may prevent colonization of organisms by interfering with adherence of microbes to mucous membranes, which may also explain their findings of pain reduction. Others have reported effects of sucralfate on chemotherapy-induced mucositis (*132,133,138*). The results of this preliminary study are encouraging.

Late Radiation Changes

Reaction in tissue may occur early due to direct toxicity of radiation. Reactions may also occur late, leading to potential complications that have as their common pathogenesis vascular damage and tissue ischemia (*139,140*). Late reactions occur at a relatively constant dose for most tissues, as reflected by the Ellis formula and other isodose calculation methods for tissue tolerance (*139–143*). High rates of complication occur above 2,000 rets (*141–143*). The dose–effect response for supporting tissue relates to radiation damage to connective tissue elements, including fibroblasts and vascular tissue (*78,144*). Late radiation changes lead to the underlying risk of osteoradionecrosis due to the resulting hypovascular and hypocellular matrix. Late changes are seen in salivary glands due to vascular damage associated with fibrosis, neurologic damage, and damage to duct structure and cellular elements of the acini (*145–151*). The underlying mechanism of radiation change is initial vasodilation due to histamine release from mast cells and increase in capillary permeability (*152*). Late changes involve endothelium, whose cell cycle is about 2 to 3 months (*153*). After radiation, some endothelial cells are damaged or die, exposing basement membrane and collagen, which activate the extrinsic clotting mechanism. The remaining viable endothelial cells proliferate abnormally, producing irregularities in the intimal wall, predisposing to thrombosis and vascular occlusion (*139*). Prostaglandins or their immediate precursors may have a significant role in the pathogenesis of acute salivary gland cell death after irradiation (*154*). Endarteritis is typical of late radiation damage (*139,153,155*).

Acetylsalicylic acid (ASA) has the potential to prevent late radiation changes due to effects on prostaglandins and their immediate precursors by inhibiting the oxidation of arachidonic acid. Another action of ASA that may be of importance is decreasing platelet adhesiveness and inhibiting the formation of platelet thrombi. ASA may affect the formation of microvascular thrombi that occur following radiation and thus reduce damage to the circulation and decrease late fibrotic change. In animal models and in preliminary human clinical trials, low-dose oral ASA was shown to decrease the radiation dose effect on stromal tolerance by 20% (*156*). Inhibition of prostaglandin synthesis by ASA and indomethacin was shown to have a role in preventing salivary gland cell death after irradiation (*154*). Continued study of ASA and related agents appears to be indicated in order to assess their potential to prevent radiation-associated microvascular change and reduce the risk of osteoradionecrosis, xerostomia, fibrosis of muscles, and other late complications associated with radiation therapy.

Other Agents

Topical folinic acid has been studied in patients who developed methotrexate-associated mucositis (*157–159*). The results of these reports are controversial, and further controlled study is required to determine whether topical application can reduce the oral toxicity of methotrexate.

The effect of beta-carotene on mucositis induced by combined radiation and chemotherapy has been evaluated in one study (*160*). Beta-carotene is a pro-vitamin A compound and is thought to be a consumer of oxygen. Patients were hospitalized and placed on a beta-carotene supplement (250 mg) for 21 days or a control diet. Twenty patients were studied, and no effect on tumor response was seen. The difference in acute mucositis was statistically significant ($P < .025$). The late mucositis reaction was not different between the groups. A lack of toxicity was seen, and no effect on recurrence or survival was seen. Continuing the beta-carotene supplement throughout radiotherapy may be more likely to reduce mucositis for the duration of treatment, and this approach appears to be of interest for further study.

MANAGEMENT OF XEROSTOMIA

Saliva has a role in maintaining the integrity of the mucosal surface and in limiting colonization and infection of the oropharynx. It is a principle of external-beam head and neck radiotherapy that the salivary glands should be excluded if possible from the primary dose. In patients who develop xerostomia, stimulation of saliva flow may reduce the difficulty with mucositis; complications of the shift in the oral flora, including increased risk of caries; and candidiasis. Preliminary study of the use of sialogogues indicates that resting and stimulated saliva can be improved in patients with xerostomia of long duration following radiotherapy (*18,161,162*). Pilocarpine has been shown to stimulate salivary flow and increase saliva production in radiation patients (*78,161,162*). Epstein and Schubert (*18*) reported a phase I-II trial of the combined use of pilocarpine and anetholtrithione (Sialor; Herdt Charton, Montreal, Canada) in patients who had not responded with increased saliva production to any single modality. A statistically significant increase in salivary volume and improved symptoms were reported. Further double-blind clinical studies of saliva production and of salivary constituents in patients using these agents may provide more information on the effects of stimulation on the complications of xerostomia. There has been no study of the use of sialogogues prior to and during radiation therapy to determine whether prevention of xerostomia is possible.

SUMMARY

It is highly desirable to prevent colonization and thus infection in the oropharynx and to prevent systemic infection. Conclusions about antibacterial, antifungal, and antiviral prophylaxis as well as prevention of mucositis must be made at this time with caution; conflicting results have been seen in past studies, and thorough, well-designed double-blind studies are needed. Many of the studies reviewed may not have been completed in a double-blind manner. Assessment of tissue reactions may have been done only via a global rating scale (none, minimal, moderate, severe). Compliance is frequently a problem, and assessment of the use of the topical agent in the

clinical setting is not well controlled in most studies. Many patients who are severely ill are unwilling or unable to comply with oral rinsing or use of oral tablets.

There have been no consistent findings of the value of chlorhexidine in reducing mucositis in studies of patients being treated for cancer. There has also been no consistent finding of prevention of colonization by bacterial pathogens or fungi. Prevention of septicemia and fungemia has not been demonstrated in the majority of studies. Many studies have been difficult to compare due to differences in the concentration and frequency of rinses. Chlorhexidine probably works to prevent mucositis by affecting the microbial flora. However, the principal effect may not be on the primary etiology of mucositis, but on secondary microbial irritation of already affected tissue. Studies by McGaw and Belch (*67*), Ferretti and others (*69,70*), Weisdorf and others (*74*), and findings at my institution suggest the need for further study of the potential of chlorhexidine to reduce oral colonization by *Candida* spp., reduce oral flora, and possibly reduce the risk of systemic infection. Further study is needed to determine whether chlorhexidine rinse may become an important adjunct in managing patients at high risk of developing mucositis and infection during treatment for cancer.

Benzydamine has consistently been shown to have the potential to reduce the severity of oral mucositis (*126,127,163,164*). Study of the prophylactic use of sucralfate suspension appears warranted, as it has the potential to protect the mucosa (*132–134,165*).

Future directions include thorough double-blind studies of pathogenesis and study of preventive therapy. The effects of topical local therapy to prevent or treat complications must be studied. The effect of oral hygiene on complications requires further study. A standard assessment tool for pain, tissue breakdown, and nutritional status is needed. Animal models may facilitate the assessment of preclinical studies. However, clinical trials in a controlled environment are needed.

Mucositis associated with radiotherapy occurs in a predictable fashion related to dose and fractionation of radiotherapy. As mucositis associated with radiotherapy is a predictable complication, it is an appropriate model for the study of preventive management. Mucositis associated with radiation therapy for cancer will provide a model of mucosal inflammation that may occur in other conditions with a less predictable course, such as that associated with chemotherapy, BMT, infection, and immune system-mediated conditions.

Much of the discussion has encompassed a review of preliminary or initial studies of medications that may be useful in preventing colonization, mucosal infection, or mucositis resulting in an increased susceptibility to infection. Studies present conflicting results for some medications and represent preliminary work in the case of other agents. Further double-blind, well-controlled studies are needed to ascertain whether preventive approaches are of value in preventing infection or mucositis. There are some encouraging studies and agents that require additional work before routine preventive approaches will be applicable for all patients who are at risk of infection during BMT or radiation therapy to the head and neck region.

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Pretherapy Interventions To Modify Salivary Dysfunction

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Salivary gland dysfunction is a common side effect of cancer therapies. Salivary secretions are reduced rapidly after starting head and neck radiotherapy. Salivary gland dysfunction has also been linked to bone marrow transplantation and to cytotoxic chemotherapy. Salivary gland stimulation during radiation has been suggested as a means of reducing radiation damage. Results of an ongoing study investigating the effects of pilocarpine on radiation-induced salivary gland dysfunction suggest that parotid function was preserved, but not submandibular/sublingual function. Also, patients receiving pilocarpine had less frequent oral complaints. Further research is necessary to develop means of preventing or alleviating the salivary side effects of cancer therapies. [NCI Monogr 9:87–90, 1990]

Salivary gland function is frequently compromised as a result of cancer therapy (*1*). Normal salivation is an essential component of oral health due to its important contributions to oral defense mechanisms and digestive functions (*2*). Lack of saliva may lead to oral hard and soft tissue lesions, including dental caries and mucosal alterations. Taste and swallowing functions may also be severely impaired in the absence of saliva. These disorders compromise not only the biological integrity of the individual, but also the general quality of life and well-being (*3*).

The health status of patients undergoing cancer therapy is obviously compromised. These patients are often immunosuppressed, and their oral mucosa is also directly affected by chemotherapy and radiation (*4,5*). Therefore, reduced salivary output in already compromised patients may have an additive deleterious effect on oral tissues. It is reasonable to assume that maintenance of normal salivary gland function in the course of therapy and thereafter may partially alleviate the numerous adverse effects often associated with these treatments.

This report discusses different approaches to prevention and management of salivary problems during cancer therapy, including an ongoing research protocol at our clinic.

RADIATION THERAPY

The effects of radiation on salivary glands have been well documented (*6*). The result is a rapid and often irreversible loss of salivary fluid secretion secondary to the severe glandular tissue damage caused by ionizing radiation (*7,8*). Along with diminished salivary output, compositional changes have been described, such as decreases in secretory IgA and sodium concentrations and in salivary buffering capacity and pH (*9,10*). Other oral sequelae of head and neck radiation, such as radiation caries, mucosal alterations, and taste disorders, have been linked to lack of normal salivation (*7,11,12*).

The dose of radiation and the amount of glandular tissue exposed to radiation are key factors determining the degree of salivary function impairment. Usually, the cumulative dose used to treat head and neck solid tumors is beyond 60 Gy, which is enough to provoke the loss of at least 80% of salivary gland function (*7,10*). The amount of glandular tissue spared (not included in the radiation field) may be crucial in determining the level of residual salivary gland function (*13*). The initial salivary flow was also reported to be an important factor in determining the residual flow rate after radiotherapy. According to one study, the higher the initial flow rate, the higher the residual flow rate (*13*).

It is generally accepted that acinar cells are most susceptible to irradiation (*14*). However, in a study testing acute irradiation in rats, biochemical mechanisms of surviving parotid acinar cells related to secretion were found to remain intact when assessed in vitro, although in vivo saliva output was diminished by more than 50% (*15*). Surviving acinar cells retained the ability to respond normally to muscarinic receptor activation. The results of this study suggest that extracellular damage, such as a neurotransmitter deficiency or interference with the system of transmission, could also play a role in radiation-induced glandular dysfunction. Accordingly, an exogenous secretagogue could compensate for this putative lack of adequate cell stimulation.

Studies of thyroid cancer patients suggest that some of these patients may develop acute and chronic salivary dysfunctions following administration of high-dose iodine (*16*). The use of salivary stimulants during therapy to reduce radiation exposure to the salivary glands was recommended (*17,18*). Although the mechanism of salivary gland damage is different for iodine and external-beam radiation, the concept of limiting salivary gland damage by enhancing salivary clearance of locally accumulated toxic products through functional stimulation is similar for both types of damage.

We are currently evaluating whether continuous salivary gland stimulation throughout the course of head and neck irradiation prevents or attenuates the deleterious effects of such therapy on salivary function, including the effects on salivary flow rate and composition both during and following radiotherapy. The secretagogue used is the parasympathomimetic drug pilocarpine, which has been shown to be effective in increasing saliva output in patients following radiation therapy (*19*) and in hypofunction of other causes, such as Sjögren's syndrome (*20*). Another important objective of this study is to determine

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whether pilocarpine use alters the effects of radiation on the oral soft and hard tissues and reduces patients' oral complaints during radiation treatment.

Patients are randomly assigned in a double-blind manner to receive either pilocarpine (5 mg) or placebo (both prepared by the National Institutes of Health Pharmaceutical Development Section). Patients are instructed to take one capsule every 4 hours, four times a day. The times of drug or placebo intake are adjusted so that medication is taken 1 hour before the daily radiation treatment session. The peak secretory effects of pilocarpine are assumed to occur within 1 hour after its intake (*20*) and therefore to coincide with the time of radiation treatment.

Drug treatment is started 1 day before the beginning of radiation therapy and continued daily for 13 weeks. Subjects are seen after the third and sixth radiation treatments and then weekly until the 13th week. At each visit, the oral cavity is inspected and the degree of mucositis is scored. Major salivary gland secretions are collected from parotid and submandibular/sublingual (SM/SL) glands. A sample of whole saliva (expectorated) is obtained as well to quantitate mucositis by albumin levels (*5*). A structured questionnaire is used to ask about oral dryness, pain, swallowing, and taste. Further examinations are performed at months 4, 5, 6, and 12.

Six patients have completed the study medication schedule and have been followed for 5–12 months. Three were assigned to placebo and three to pilocarpine. Although small, the study sample is well balanced for sex, age, and the amount and field of radiation to which the major salivary glands were exposed. Drug-related adverse effects were not reported by any patient.

Stimulated parotid flow tended to be maintained as a result of pilocarpine administration (fig. 1).

The observed preservation of parotid function is of particular interest in light of reports pointing to the parotid as the more radiosensitive gland (*14*). It is not clear, however, whether the effect is due to stimulation of the spared portion of parotid tissue or the result of radioprotection of irradiated portions of the glands. The positive long-term effect, beyond the 13-week period of study medication administration, suggests that at least

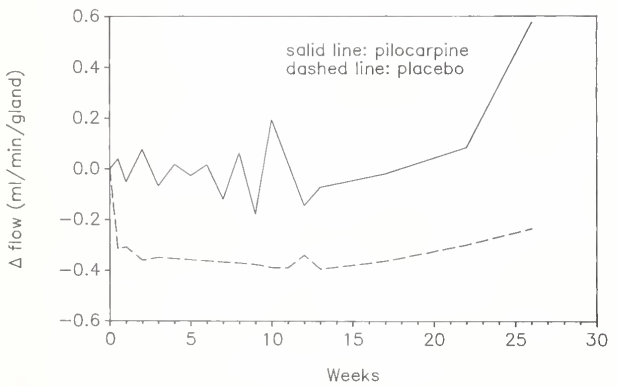

FIGURE 1. Changes in stimulated parotid flow. Values are means of changes in flow rates at each visit for pilocarpine- and placebo-treated patient groups. Change values were obtained by subtracting the baseline flow value from the flow value determined at follow-up visits. Flow was stimulated with 2% citric acid applied to anterior dorsolateral tongue surfaces at 30-sec intervals.

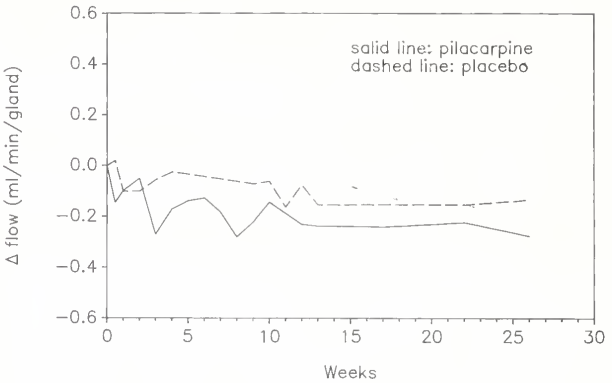

FIGURE 2. Changes in stimulated SM/SL flow. Values are means of changes in flow rates at each visit for pilocarpine- and placebo-treated patient groups. Change values were obtained by subtracting the baseline flow value from the value determined at follow-up visits.

part of the maintained function derives from better-functioning irradiated tissue compared to the placebo group.

Conversely, pilocarpine did not show a similar preservative effect on SM/SL salivary flow parameters (fig. 2). Whether this lack of effect is due to the total inclusion of SM/SL glands in the radiation field or to less reactivity of those glands to pilocarpine compared to the parotid glands is not known. The major salivary glands differ in their structure, e.g., the submandibular and sublingual glands have a large proportion of mucous secretory units, whereas the parotid glands' acinar cells are serous (*21*). Some differences in agonist sensitivity may exist for these cells.

We know that the sample is too small to draw definitive conclusions. However, the results suggest that pilocarpine was beneficial in maintaining parotid gland fluid secretion during radiation. Additionally, there was a marked decrease in many of the subjective oral complaints related to radiation (data not shown).

While saliva is important to maintain oral hard and soft tissue integrity, it is not the only protective factor. Radiation also directly affects other tissues of the oral cavity and the commensal flora (*11,12*). Therefore, a broader approach to protect oral tissues from ionizing radiation is needed. Meticulous oral hygiene and topical fluoride applications should be included in the routine of clinicians involved in any cancer treatment with oral side effects (*22–24*). Shielding prostheses that block radiation exposure of oral areas not involved with the tumor have been designed (*25*). However, no systematic studies on the oral tissue-preservative effects of these devices have been published. Systemic administration of beta-carotene during a course of intensive combination chemotherapy and radiotherapy for advanced head and neck epidermoid tumors has been suggested as useful to protect mucosal membranes located within the radiation fields (*26*). Chlorhexidine and benzydamine mouthwashes have also been given to head and neck radiation patients to control overall pain and mucositis (*27*). However, data on the efficacy of these compounds are still sparse, particularly regarding their ability to suppress *Candida* species and growth of coliforms.

Other approaches to prevent radiation damage to salivary glands include the use of radioprotective agents. A study of Amifostine (also known as WR-2721) was promising. A greater percentage of Ga scintigram-negative salivary glands were found in patients pretreated with this agent than in patients not so treated (*28*). These results could indicate that Amifostine has a protective effect on salivary tissues. Clinical trials, however, have been limited by its toxicity (*29*), and salivary gland output and composition have not been studied yet. Several laboratories reported radioprotective effects of compounds such as glucan (*30*) and cysteamine derivatives (*31*), but these studies were restricted to animal models and the effect of most of these compounds on salivary gland function is not known. Other investigators have noted that activation of beta-adrenergic receptors with isoproterenol in rats prevented radiation-induced weight loss of parotid glands (*32*).

OTHER CANCER THERAPIES

The salivary gland effects of other cancer treatments are less frequent and not as well characterized as the changes induced by head and neck radiation. The occurrence of a Sjögren's-like syndrome following bone marrow transplantation has been described (*33*). Salivary gland impairment, seen in some of these patients, may also be caused in part by pretransplant conditioning with total-body irradiation (*1*). Palliative measures have been proposed to alleviate this type of xerostomia, including the use of artificial salivas, oral lubricants, and sialogogues (*24*). Prevention of salivary gland dysfunction as a result of bone marrow transplantation merits further investigation.

Oral changes due to cytotoxic therapy, in particular oral mucositis, have been described (*4*). Although many patients complain of xerostomia, data on salivary gland function disturbances in cancer chemotherapy patients are not consistent. Whole-saliva volume in these patients was found to be decreased (*34*) or unchanged (*35*). A study of individual gland function showed that parotid and SM/SL saliva values did not vary significantly during chemotherapy from pretreatment values (*1*). Several investigators have shown qualitative changes in saliva (*1,34,35*), but no evidence is available on the relationship of these changes to the frequent mucosal alterations seen in chemotherapy patients. This area also demands further research.

Finally, salivary gland tumors and surgical removal of these tumors occur relatively infrequently. Studies in this area have concentrated mainly on postsurgical complications, such as nerve palsies, sialoceles, and salivary fistulas, rather than on the impact of salivary gland removal on overall salivary gland function (*36*). It is likely that the extent of this impact is related to the amount of glandular tissue removed and that, in accordance with this, residual overall salivary gland function can be predicted. A compensatory proliferative response of rat submandibular glands to unilateral extirpation has been described (*37*). Clinical studies should be initiated to investigate whether such responses also occur in human salivary glands.

SUMMARY

In summary, salivary gland dysfunction is a frequent adverse effect of cancer therapy. This demands the exploration of means to prevent or attenuate this problem to help improve patients' cancer treatment, health status, and quality of life.

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IV. Management of Acute Problems

Studies on the Prevention of 5-Fluorouracil-Induced Oral Mucositis

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Oral mucositis is a major toxic effect related to 5-fluorouracil (5-FU) therapy. Clinical studies have attempted to identify an effective antidote for this untoward side effect. Early pilot studies suggested that an allopurinol mouthwash could lessen 5-FU-induced mucositis. However, a randomized, double-blinded, placebo-controlled crossover study did not suggest that an allopurinol mouthwash had any prophylactic value in this clinical situation. An ongoing, randomized clinical protocol is testing cryotherapy as a method of inhibiting 5-FU-induced stomatitis. No clinically appropriate prophylactic measure for preventing 5-FU-induced mucositis has been found to date. [NCI Monogr 9:93–94, 1990]

Oral mucositis is a major dose-limiting toxic effect of 5-fluorouracil (5-FU), a frequently used cytotoxic drug for the treatment of several human malignancies. Although this toxicity is usually not life-threatening, 5-FU-produced oral ulcerations can be quite painful and may have a significant impact on patient nutrition and quality of life. The incidence of 5-FU-induced stomatitis appears to be related to a number of factors. More mucositis is seen with higher 5-FU doses, a continuous intravenous infusion schedule (as opposed to intermittent bolus doses) (*1*), the use of other mucositis-producing cytotoxic drugs (such as methotrexate and doxorubicin), and the concurrent use of leucovorin given to augment 5-FU cytotoxicity (*2*).

An effective prophylactic method for alleviating 5-FU-induced mucositis would have the potential to significantly enhance patient comfort and nutrition and might also allow greater antitumor activity if higher doses of 5-FU could be given safely. Studies have therefore been initiated to evaluate whether 5-FU-induced mucositis can be prevented by the use of an allopurinol mouthwash or by the use of cryotherapy. Current data from these investigations are presented in this article.

ALLOPURINOL MOUTHWASH

Systemically administered allopurinol appears to decrease 5-FU toxicity and allow the safe administration of higher 5-FU doses (*3–5*). It has been hypothesized that allopurinol ameliorates 5-FU toxicity by inhibiting the enzyme orotidylate decarboxylase and thereby decreasing the formation of the 5-FU metabolites fluorodeoxyuridine monophosphate and fluorouridine triphosphate. Based on these findings, an allopurinol mouthwash has been tested as a way to prevent 5-FU-associated mucositis. Clark and Slevin (*6*) reported that an allopurinol mouthwash decreased the severity of mucositis in six of six patients who had developed mucositis following an initial cycle of chemotherapy with 5-FU alone. When an allopurinol mouthwash was administered immediately and 1, 2, and 3 hours after 5-FU administration, stomatitis was not seen in three patients and was significantly ameliorated in the other three patients when a second course of 5-FU was given at the same dose level. Based on the results of this report, the use of an allopurinol mouthwash became incorporated into clinical practice in some institutions (*7,8*).

Subsequently, a Mayo Clinic–North Central Cancer Treatment Group (NCCTG) randomized, double-blinded, placebo-controlled, crossover trial was completed to determine whether this allopurinol mouthwash was of value (*9*). Seventy-seven patients receiving their first cycle of 5-FU (with or without leucovorin) were stratified and then randomized to receive an allopurinol or placebo mouthwash. The dose and schedule of allopurinol in this study were similar to those used in the initial pilot study of Clark and Slevin (*6*). In this randomized study, 30 mL of a 1-mg/mL allopurinol solution (or placebo) was swished around the oral cavity for 30 seconds and then discarded (not swallowed). The mouthwash was used every hour for four doses, commencing with each of five consecutive daily doses of 5-FU. Prior to the initiation of this study, it was determined that this mouthwash procedure did not result in any measurable systemic concentration of allopurinol or its major metabolite, oxypurinol, which theoretically might inhibit the antitumor activity of 5-FU (*10*). Unfortunately, the results of this randomized study were convincingly negative; there was a trend (not statistically significant) for patients receiving the allopurinol solution to have more mucositis than the patients who received the placebo mouthwash. Of 20 patients who crossed over from allopurinol to placebo or vice versa, there again was a nonsignificant trend toward more mucositis with the allopurinol solution (most of the 77 original patients did not cross over because of an alteration in their initial 5-FU dose for such reasons as 5-FU toxicity, lack of 5-FU toxicity, or disease progression).

Recently, a nonrandomized pilot study in Greece suggested that an allopurinol mouthwash alleviated 5-FU-associated mucositis in 16 of 16 patients who had mucositis after receiving a previous cycle of 5-FU (*11*). This trial was different from the previous two trials in that (*a*) the 5-FU was administered as a 5-day continuous intravenous infusion (as opposed to daily bolus doses), (*b*) a 16-fold-higher allopurinol concentration (16 mg/mL) was used, and (*c*) the mouthwash was retained in the oral cavity for 5 minutes (as opposed to ≤30 sec) four to six times per day (as opposed to four doses given hourly). If an allopurinol concentration of 16 mg/mL is administered four to six times per day, relatively standard mouthwash volumes of 5–20 mL/dose (the actual volume used in this study was not reported in the manuscript) would result in the daily administration of 320–1,920 mg of allopurinol (in contrast to a usual daily oral dose of 300 mg). The article stated that patients were

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instructed not to swallow the mouthwash, but a fraction of it was surely swallowed as each dose was to be retained in the oral cavity for 5 minutes. It is recommended that this mouthwash procedure should not be incorporated into routine clinical practice without (*a*) determining whether this allopurinol administration schedule results in systemically detectable levels of allopurinol or its major metabolite, oxypurinol (as this may interfere with the antitumor activity of 5-FU), and subsequently (*b*) confirming this pilot study's results by a controlled clinical trial.

CRYOTHERAPY

The serum half-life of 5-FU following bolus intravenous drug administration is in the 10–20-minutes range (*12*), while its tissue half-life may be about 24 hours (*13*). It is a reasonable hypothesis that mouth cryotherapy around the time of intravenous 5-FU bolus administration could (*a*) cause local vasoconstriction, (*b*) result in decreased blood flow to the oral mucous membranes during the period of peak serum 5-FU concentration, and (*c*) subsequently produce a decreased incidence and severity of 5-FU-induced mucositis. This would be in concert with data demonstrating that scalp cryotherapy decreases chemotherapy-associated alopecia (*14*). Unpublished investigations have determined that continuous sucking on ice chips for 30 minutes does not cause significant toxicity in most patients and that, not surprisingly, this procedure decreases the temperature of the mouth. Preliminary, uncontrolled observations suggest that sucking on ice chips may lessen mucositis after 5-FU administration (*15*). Currently, a Mayo Clinic-NCCTG protocol is examining this cryotherapy procedure. Patients receiving their first course of bolus 5-FU and leucovorin are being randomized to receive standard care versus cryotherapy (oral ice chips for 30 min starting 5 min prior to each 5-FU dose). These patients are subsequently followed up for mucositis incidence and severity. The results of this study should be available in 1990.

CONCLUSION

5-FU-induced mucositis continues to be a major problem, with no established antidote at this time. Hopefully, cryotherapy, a relatively nontoxic and inexpensive endeavor which is actively being investigated, will produce positive results. Although a randomized trial of allopurinol mouthwash use resulted in convincingly negative data, it may be that a different allopurinol dose or schedule could prove to be helpful. Other 5-FU-modulating agents, such as thymidine, uridine, and cytidine (*16*), might be worth testing as prophylactic measures for alleviating 5-FU-induced mucositis.

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Management of Mucositis During Therapy

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This paper reviews the purposes of an oral care protocol, the major components of an oral care regimen, and oral care protocols and studies done to date. Many questions remain in the area of optimal oral care for the patient experiencing mucositis as a sequela of cancer treatment. Research is needed on types and use of mouth rinses, effective, harmless, and pleasant lip lubricants, appropriate analgesic and anti-inflammatory combinations, and the effectiveness of a variety of devices for oral cleansing, to name a few areas. As outpatient oncology services grow, oral care protocols must be developed to meet the needs of ambulatory patient populations. Oral care regimens must be safe, easy to use, and economical as well as effective to ensure patient and staff compliance. Research on the management of mucositis must be conducted in both inpatient and outpatient settings. Finally, in order to obtain sufficient sample sizes and optimize data collection, these studies will need to be conducted by multidisciplinary teams (including dentists, oncologists, radiation therapists, and nurses) across multiple sites. Not until large-scale clinical trials are done on the treatment of mucositis will we be able to optimize the therapeutic regimen for the patient. [NCI Monogr 9:95–98, 1990]

Numerous reports have addressed the associated changes in the oral mucosa and the subsequent development of mucositis in patients receiving chemotherapy (*1–15*), radiation therapy (*16–21*), or bone marrow transplantation (*22–24*) for malignant disease. Changes in the oral mucosa can be as minimal as generalized erythema or progress to confluent ulcerations with or without hemorrhages. In addition, numerous complications are associated with the development of mucositis (*25–27*). These problems are listed in table 1.

Patients are at risk for local infections, experience pain and discomfort that are often associated with a decrease in nutritional intake, and often describe a generalized decrease in well-being. In addition, more serious problems or complications can occur. Patients can develop systemic infections after the development of mucositis. In some cases, the oral ulcerations and associated discomfort are so severe that they necessitate a reduction in chemotherapy dose or radiation therapy or the cessation of therapy altogether. This can markedly alter the patient's prognosis. In addition, oral mucositis and the associated increase in morbidity can contribute to increased length of hospitalization and costs of treatment. A proactive, aggressive, and systematic treatment plan must be developed for patients with mucositis.

This article reviews the current management of mucositis related to cancer treatment. The article will evaluate oral care protocols used in clinical practice. Emphasis will be placed on a critique of current treatment modalities, major gaps in research-based practices, and implications for future research.

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PURPOSES OF AN ORAL CARE PROTOCOL

Oral care protocols should be developed and implemented to maintain the integrity of the oral mucosa, keep the lips clean, soft, moist, and intact, prevent dental caries and periodontal disease, alleviate oral pain and discomfort, prevent or treat infectious complications, and ensure the maintenance of adequate nutritional intake (*27*). These six objectives could serve as uniform criteria to evaluate the efficacy of a variety of oral care regimens. To date, only a limited number of clinical studies have attempted to systematically measure the effectiveness of various aspects of oral care protocols. However, there have not been any large-scale clinical trials to evaluate the efficacy of different types of oral care regimens with a complete set of objective monitoring criteria.

COMPONENTS OF AN ORAL CARE REGIMEN

Analysis of the major components of oral care protocols that have been published to date shows four major types of interventions. The first group is aimed at cleansing the oral mucosa. This is achieved through the use of a variety of cleansing agents and devices. The frequency with which these cleansing regimens are performed is often based on the severity of the mucositis, patient compliance, or the availability of nursing personnel. The second set of interventions are aimed at maintaining the moisture of the lips and oral cavity. The third group of interventions center on relieving pain and inflammation. A variety of "mixtures" aimed at providing anesthesia, analgesia, and coating to the oral mucosa have been described in the literature. However, there have been no controlled studies comparing the efficacy of any of these combination regimens in relieving inflammation or enhancing patient comfort. The last group of interventions center on measures to prevent or treat infection and are not discussed in this article.

A review of the literature on the treatment of mucositis leaves two general impressions of the approach to the management of this problem: the first is that if a little is good, then a lot is better, and the second is that every possible agent must be used to treat every aspect of the problems associated with mucositis. Beyond these broad overall impressions, systematic review of the efficacy of the limited number of oral care protocols published in the literature is fraught with difficulty. First, the assessment parameters and criteria used to measure the efficacy of various treatment regimens are inconsistent. The oral care protocols vary tremendously in terms of types of cleansing agents used, frequency with which the agent is administered, and whether or not adjuvant measures are employed. In addition, patient populations are not homogeneous. The samples are small and vary in overall treatment, i.e., chemotherapy or radiation therapy, and within the chemotherapy group patients often receive a variety of stomatotoxic regimens. With these major limitations in mind, I will attempt to evaluate the research in the area of oral care

Table 1. Problems associated with mucositis

Local infections
Pain and discomfort
Decreased food intake
Decreased sense of well-being
Systemic infections
Decrease in dose or cessation of therapy
Longer hospital stay

protocols published to date by considering each component of the protocol and identifying questions that require further investigation.

Cleansing Agents and Devices

Based on a review by Daeffler (*28*) published in 1980, the three major cleansing agents used in cancer institutions are hydrogen peroxide and water, normal saline, and sodium bicarbonate solution. Hydrogen peroxide is generally diluted with four parts water immediately prior to use (*29*), although other dilutions have been reported (*28*). It is noted that hydrogen peroxide should not be used when a patient has fresh granulation surfaces in the mouth because it tends to break down new tissues (*30*). Segelman and DoKu (*31*) suggest that hydrogen peroxide not be used for leukemic gingivitis because it could cause overgrowth of fissures and white papillae of the tongue that could provide an excellent base for candidiasis.

Saline mouthwashes have been recommended for the treatment of leukemic gingivitis (*31*) and for patients having head and neck irradiation (*32*). They are known to be safe and economical. Sodium bicarbonate has also been used as a cleansing agent because of its ability to dissolve mucus and loosen debris (*33*). No studies to date have evaluated the optimal dilution of either saline or sodium bicarbonate or whether these mouthwashes are more efficacious when used as single agents, alternated, or used in combination. The optimal mouthwash to be used in the treatment of mucositis has not been determined.

A variety of cleansing devices have been used in the management of mucositis (table 2). DeWalt (*34*) reported a study of timed hygiene measures in a group of geriatric patients. Comparisons of a toothbrush and a toothette showed that the toothbrush was more effective in stimulating gingival tissue and removing debris and that the toothette was more effective in producing improvement in other oral tissues. Most oral hygiene regimens for oncology patients that are described in the literature recommend the use of a soft toothbrush and unwaxed dental floss unless it is contraindicated by pain and bleeding (*26*). Questions arise, however, as to the optimal frequency for cleansing the oral cavity of patients who cannot perform this activity themselves.

Table 2. Oral hygiene cleansing devices

Toothbrush, soft
Toothettes
Gauze
Irrigation devices

The use of lemon-glycerin swabs has been studied by several investigators (*35,36*). Van Drimmelen and Rollins (*36*) found that lemon-glycerin swabs were not adequate for cleansing the oral mucosa. In addition, it was noted that the lemon juice and glycerin tended to dry the oral mucosa. This would be an undesirable side effect in patients predisposed to or experiencing mucositis. The use of lemon-glycerin swabs is therefore contraindicated for patients who may develop or actually have mucositis.

Lubricants

Lubricants must be used to keep the lips clean, moist, and intact. The most commonly used lubricants are K-Y Jelly, Vaseline, and mineral oil (*28*). In addition, some institutions reported the use of artificial saliva to combat the problems of xerostomia associated with radiation therapy. Daeffler (*26*) points out that research is needed to find a safe, harmless, and effective lip lubricant. Both petroleum jelly and mineral oil are potentially harmful if aspirated and should be used with caution. Water-soluble lubricating jelly may be used on the lips as well as on the oral mucosa, but its effectiveness has not been established through scientific studies.

Anesthetics, Analgesics, and Mucosal Coating Agents

The most common anesthetics, analgesics, and mucosal coating agents used in the treatment of mucositis are listed in table 3. These agents are often administered in therapeutic mixtures. Some examples of mixtures reported in the literature are Benadryl (diphenhydramine hydrochloride), Kaopectate, and milk of magnesia; Benadryl and Kaopectate; Benadryl and viscous Xylocaine (lidocaine); Maalox and viscous Xylocaine; and Benadryl, Maalox, and viscous Xylocaine. All of these combinations were devised and used based on clinical judgment. There is no experimental evidence to support the efficacy of one combination over another. Whether these combinations are meant to be used as topical rinses (i.e., swish and spit) or ingested (i.e., swish and swallow) to have maximal therapeutic effects against mucositis has not been addressed.

ORAL CARE PROTOCOLS

An evaluation of oral care protocols from a variety of institutions reveals several common characteristics (*37,38*). First, all protocols include some type of assessment of the oral mucosa. The frequency with which this assessment is to be performed by nursing personnel is highly variable. The second characteristic is that most protocols tend to have levels based on the severity of the mucositis. Although the definitions of severity vary, there is usually some type of routine oral care

Table 3. Anesthetics, analgesics, and mucosal coating agents

Benadryl (diphenhydramine hydrochloride)
Dyclonine hydrochloride (Dyclone)
Kaopectate
Milk of magnesia
Orabase
Viscous Xylocaine (lidocaine)
Benzydamine hydrochloride
Systemic analgesics

Table 4. Characteristics of oral care protocols

1.	Oral assessment — treatment based on findings
2.	Routine oral care
	Performed four times per day, usually after meals and before sleep
	Components of oral care regiment: flouride toothpaste, soft toothbrush, dental floss, lip lubricant
3.	Oral care for mild stomatitis
	Culture of the oral cavity
	Complete blood and differential counts
	Bland diet
	Oral hygiene measures every 2 hr, including mouthwash
	Topical analgesics and/or anti-inflammatory agents
	Topical antibiotics as ordered
4.	Oral care for severe stomatitis
	Culture of the oral cavity
	Complete blood and differential counts
	Oral hygiene measures every hour while awake, alternative types of mouthwashes
	Use of topical anesthetics, analgesics, and antibiotics

regimen and then regimens for mild and severe mucositis. A sketch of the common characteristics of oral care protocols is shown in table 4.

The routine care oral care protocol is usually performed three times a day and before sleep. Most oral care protocols recommend increasing the frequency of the oral care for more severe mucositis, from four times a day to every 2 hours and, in the most severe cases, to every hour. There is no scientific evidence to support the efficacy of or need for such frequent interventions.

Eleven studies have evaluated the impact of a variety of oral care protocols on the development of changes in the oral mucosa (*25,27,28,34,36,37,39–43*). While these studies were done with a variety of patient populations (i.e., healthy subjects, elderly patients, renal failure patients, and patients receiving chemotherapy) and a variety of oral care protocols or treatment regimens, one overwhelming conclusion is evident. Most of these investigators note that the systematic performance of oral care is more effective in reducing the incidence of mucositis than the types of agents or devices used. This hypothesis requires further investigation.

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Oral Complications Following Neoadjuvant Chemotherapy in Patients With Head and Neck Cancer

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Oral complications from cancer chemotherapy are well documented for the hematologic malignancies but are less well defined for cancers of the head and neck. This prospective study examined 82 patients with stage III or IV disease to determine the incidence and severity of oral sequelae following a total of 141 cycles of neoadjuvant chemotherapy. Taste alteration (37%) was the most frequent problem, followed by mucositis (30%) and ulceration (22%). Xerostomia, increased salivary flow, loss of appetite, weight loss, dysphagia, bleeding, and infection were also encountered. We conclude that oral problems are common following chemotherapy for head and neck tumors and that more aggressive investigational protocols will result in a much higher incidence and severity of problems. Prevention of these sequelae by conventional as well as investigational means is important to keep them from becoming dose-limiting problems. [NCI Monogr 9:99–101, 1990]

Mucositis, ulceration, infection, and bleeding of the oral cavity are potentially serious complications of cancer chemotherapy (*1–9*). These complications are well documented for intensive chemotherapy for the hematologic malignancies or for the purpose of bone marrow transplantation. The incidence and severity of acute oral problems depend on chemotherapy dose and schedule of administration and may increase with each course of therapy. Oral complications following chemotherapy for head and neck malignancies are less well defined (*10,11*). Neoadjuvant (induction) chemotherapy, prior to radiotherapy (RT) and/or surgery, is a common investigational therapy for patients with head and neck cancer (*12*). Complete clinical response rates of up to 50% have been reported with initial chemotherapy in patients with advanced tumors (*13,14*).

The apparent activity of neoadjuvant chemotherapy in this setting has encouraged further intensification of treatment protocols. Some of the agents most commonly used for head and neck tumors (e.g., methotrexate, bleomycin sulfate, cisplatin, and 5-fluorouracil) are stomatotoxic when used alone and in combination are more likely to result in dose-limiting stomatitis. The identification and management of oral complications associated with chemotherapy therefore becomes important, given the influence of drug dose on response to treatment.

This prospective study was undertaken to determine the nature, frequency, and severity of oral complications following neoadjuvant chemotherapy in patients with head and neck cancer.

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METHODS

Eighty-two patients, 60 males and 22 females, with untreated stage III or IV head and neck cancer were entered into the study following initial evaluation in a multidisciplinary head and neck tumor clinic with participants from otolaryngology, radiation therapy, medical oncology, and dentistry. Seventy-six patients had squamous cell carcinomas, and six had malignancies of other histologic types. All patients were entered into a protocol study of neoadjuvant cisplatin, bleomycin, and methotrexate therapy. Up to three cycles of chemotherapy were administered prior to surgery or RT. Oral examinations were carried out for all patients upon entry into the study. Examinations consisted of a charting of existing and missing teeth and a clinical assessment of the degree of gingivitis or periodontitis, caries, and soft tissue problems, all done with tongue blade and flashlight. Repeat oral examinations were done prior to and following each cycle of chemotherapy, and the information on the following problems was gathered: xerostomia, mucositis, ulceration, bleeding, infection (fungal, bacterial, or viral), loss of appetite, weight loss, taste alteration, and dysphagia. The severity of mucositis and ulceration was graded as follows: 1 = mild (no limitation of function or intake); 2 = moderate (function or oral intake limited, but medication not required); 3 = moderately severe (function limited and medication required); 4 = severe (requiring medication—no oral intake). Taste alteration, xerostomia, loss of appetite, and dysphagia were scored in the following manner: 1 =mild (bothersome but did not result in altered nutritional intake); 2 = moderate (altered nutritional intake but no resultant weight loss); 3 = moderately severe (loss of up to 10% of total body weight). Bleeding and infection were considered mild if the problem was easily managed with local (e.g., scaling, improved hygiene) or topical (e.g., antifungal rinses) measures and moderate if systemic (e.g., antibiotics) or more invasive (e.g., extraction) therapy was deemed necessary.

RESULTS

All 82 patients had at least one cycle of neoadjuvant chemotherapy. Forty-four patients had two cycles, and 15 patients had three cycles of chemotherapy. Patients were evaluated before and during a total of 141 rounds of chemotherapy. The frequency of complications during all 141 cycles of chemotherapy is listed in table 1 and in figure 1. Taste alteration was the most frequent problem, as this occurred in 53 of 141 (37%) cycles of chemotherapy. Forty-three (30%) cycles resulted in mucositis, and 31 (22%) of these involved frank ulceration. Xerostomia was reported following 33 (23%) cycles of chemotherapy. Three additional patients reported an increase in salivary flow. Twenty-five (17%) cycles of chemotherapy resulted in a loss of appetite, and 18 (12%) patients lost weight. Dysphagia was

Table 1. Overall frequency and severity of oral complications from induction chemotherapy

Complication	No. (%) of cycles (n = 141)				
	Mild	Moderate	Moderately severe	Severe	Overall
Taste alteration	19 (13)	26 (18)	8 (6)	0	53 (37)
Mucositis	17 (12)	16 (18)	7 (5)	3 (2)	43 (30)
Xerostomia	19 (13)	11 (8)	3 (2)	0	33 (23)
Ulceration	11 (8)	14 (10)	5 (4)	0	31 (22)
Loss of appetite	11 (8)	8 (6)	6 (4)	0	25 (17)
Weight loss	8 (6)	5 (4)	5 (4)	0	18 (12)
Dysphagia	4 (3)	3 (3)	1 (1)	0	8 (6)
Bleeding	4 (3)	2 (1)	0	0	6 (4)
Infection	4 (3)	2 (1)	0	0	6 (4)

reported by patients following eight (6%) cycles, although it was difficult to determine whether tumor involvement was a contributing cause. Six cycles (4%) of chemotherapy were associated with oral bleeding from gingival sites. Six cycles precipitated oral infection: four bacterial, one fungal, and one viral. Table 1 and figure 1 lists the severity of complications for all three cycles of chemotherapy combined.

An analysis of these data reveals that 11% of the chemotherapy cycles resulted in mucositis or ulceration that required medication or that severely limited oral intake. However, 26 (25%) cycles resulted in at least moderate mucositis and 19 (14%) resulted in ulceration limiting oral intake or function. Severe mucositis was a problem in three (2%) exposures. An additional 18 (13%) patients had moderately severe taste alteration, xerostomia, dysphagia, or loss of appetite that contributed to decreased nutritional intake. Although taste alteration interfered with oral intake in 34 (24%) patients, this was a transient problem that usually occurred during chemotherapy administration and resolved soon thereafter. Although 14 (10%) patients experienced a drying of the oral mucosa or a thickening of their saliva to the point of interfering with nutrition, this too was transient in nature. The three patients who complained of an increase in saliva were probably experiencing thickened saliva, difficulty with swallowing it, and resultant increased awareness of a change in their salivary composition rather than volume.

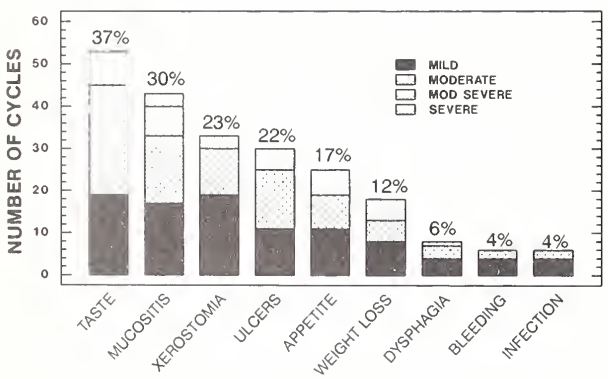

FIGURE 1. Overall frequency and severity of complications during 141 cycles of induction chemotherapy. Mod severe = moderately severe.

Coupled with and often indistinguishable from the problem of taste alteration was the problem of loss of appetite. This problem was significant (moderate to moderately severe) in 14 (10%) patients. Dysphagia was a minor problem in terms of both incidence and severity. Bleeding and infection were relatively minor problems encountered by these patients, and they were managed by conventional local measures.

A comparison of complications that occurred during each of the three cycles of chemotherapy suggests that there was no significant increase in the incidence or severity of any of these complications with each successive cycle. The number of patients for whom second- and third-cycle data are available is too small, however, for statistical assessment. In addition, several patients with moderately severe oral complications received decreased doses of chemotherapy in subsequent cycles in order to improve treatment tolerance.

DISCUSSION

The attempt to reduce the bulk of local and regional tumor tissue, as well as to eradicate microscopic distant disease, has generated considerable interest in the addition of chemotherapy to the traditional management of advanced head and neck cancer. In the past decade, considerable progress has been made in defining a role for chemotherapy as neoadjuvant or postoperative (adjuvant) treatment of this disease.

In this study of oral complications with neoadjuvant chemotherapy for head and neck cancer, nearly one-third of the chemotherapy cycles resulted in at least mild mucositis and ulceration or problems with nutrition. However, the severity of these complications was less than that usually seen with protocols for other malignancies (e.g., acute leukemia and bone marrow transplantation) (*4,15*). In general, current regimens of chemotherapy for head and neck cancer result in less frequent and less severe oral complications.

However, intensification of chemotherapy to attain increased response rates will undoubtedly result in more frequent and severe mucositis and its sequelae. This is especially true when patients receive simultaneous RT and chemotherapy or when RT follows chemotherapy within a short time period. Preliminary results from an ongoing study at the Dana-Farber Cancer Institute support the association between intensification of neoadjuvant therapy, a higher rate of response to chemotherapy, and increased mucositis (Clark JR: personal communication).

In this study, high-dose leucovorin, a known modulator of 5-fluorouracil activity, has been added to a regimen of cisplatin and 5-fluorouracil for patients with previously untreated, advanced squamous cell carcinomas of the head and neck. To date, 46 patients have completed neoadjuvant treatment, with 36 (78%) of them responding to chemotherapy, including six (13%) partial and 30 (65%) complete responses. The price of this improved rate of complete response has been increased mucositis. Of these 37 patients, 21 (57%) experienced moderate and 14 (38%) experienced severe mucositis with their first course of therapy, and 5 (14%) required hospitalization for management of this problem.

Improved pretherapy dental evaluation and treatment, along with improved methods of management of oral problems (*16–18*), are essential to keep oral complications from becoming dose-limiting such that survival is adversely affected. Recent advances in the medical management of mucositis have been achieved and include topical anesthetics (*19,20*), antifungal and antiviral agents, and improved overall mouth care. In addition, the use of recombinant human granulocyte colony-stimulating factor, a myeloid growth factor, has been associated with decreased mucositis in a trial of chemotherapy for patients with advanced bladder cancer (*21*). While it is not known how recombinant human granulocyte colony-stimulating factor limits the mucositis associated with chemotherapy, this agent is under active investigation in this and other settings where mucositis is a complication (*22*). Given the number of peptide growth and inhibitor factors with activity on epithelial cells and cells associated with the repair of soft tissue injury (fibroblasts, platelets, etc.) that are being defined, a new generation of agents capable of preventing or limiting the oral complications of chemotherapy may soon be available.

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Role of Herpes Simplex Virus Reactivation in Chemotherapy-Induced Oral Mucositis

Spencer W. Redding

Reactivation of oral herpes simplex virus (HSV) is very common in patients receiving cytotoxic chemotherapy or bone marrow transplantation. Numerous studies have shown the incidence rate of reactivation to be between 50% and 90% in these populations. Other studies have attempted to correlate oral mucositis and HSV reactivation. From 37% to 68% of all oral mucositis lesions were culture positive in mixed populations of chemotherapy and bone marrow transplant patients. The lesions that were culture positive tended to be more severe than those that were culture negative. These lesions were also atypical in that they involved any perioral and intraoral surface. Patients receiving cytotoxic chemotherapy should have any mucositis lesions evaluated for HSV, including laboratory testing, and should be treated aggressively with acyclovir. Certain groups, such as bone marrow transplant and leukemia patients who are seropositive, should be considered for acyclovir prophylaxis. [NCI Monogr 9:103–105, 1990]

Oral herpes simplex virus (HSV) infection is a very common finding in the general population. The rate of recurrent infections has been reported to be between 6% and 14% in this group. However, exposure to the virus is much higher, as evidenced by patient seroconversion. HSV antibody titers will be positive in 30%–50% of high socioeconomic groups and in 80%–100% of low socioeconomic groups (*1*).

Beginning in the early 1980s, several authors reported a high incidence of oral HSV infection in patients receiving chemotherapy or bone marrow transplantation (BMT) (table 1). Most of these patients were entered as control groups in studies testing the efficacy of the antiviral drug acyclovir. In 1980, Meyers and co-authors (*2*) reported an 82% incidence of oral HSV infection over a period of 120 days after allogeneic BMT in patients who were seropositive for HSV. Of these lesions, 64% occurred within the first 5 weeks. In 1982, Meyers and co-workers (*3*) reported an 85% incidence of oral HSV infection over a period of 49 days in a mixed immunosuppressed group of patients, including those receiving BMT, those receiving chemotherapy for leukemia or lymphoma, and those receiving renal or cardiac transplant. In 1981, Saral and co-authors (*4*) reported a 70% incidence of oral HSV infection in seropositive patients within 80 days of BMT. In 1982, Wade and co-authors (*5*) reported a 65% incidence of oral HSV infection in seropositive patients within 49 days of BMT. In 1983, Prentice and co-authors (*6*) reported that 50% of a mixed BMT and chemotherapy patient population who were seropositive developed oral HSV infection within 10 to 24 months of treatment. Infection incidence was 50% in both groups. In 1983, Gluckman and co-authors (*7*) reported a 90% incidence of oral HSV infection in seropositive patients within 100 days of BMT. In 1983, Hahn and co-authors (*8*) reported a 50% incidence of oral HSV infection in a mixed seropositive BMT and chemotherapy population within 14 months of treatment. In 1984, Wade and co-authors (*9*) reported a 73% incidence of oral HSV infection in seropositive patients within 33 days of BMT. A majority of these studies showed that the incidence rate declined to near zero in patients lacking HSV antibody, as depicted in the study by Meyers and co-authors (*2*), in which only 1.6% of seronegative patients developed HSV infection after BMT.

In the mid-1980s, several authors reported on the relationship of HSV reactivation and oral mucositis with cancer chemotherapy and BMT (table 2). Seto and co-authors (*10*) in 1985 reported that 37% of cultures from BMT patients who developed oral mucositis were positive for HSV. They also reported that mucositis associated with HSV was more severe and of longer duration than mucositis in the HSV-negative group and that lesions occurred on all mucosal surfaces of the oral cavity. Barrett (*11*) in 1986 reported that orofacial HSV infection occurred in 40% of a group of leukemia patients who received conventional chemotherapy or BMT. Oral mucosal involvement occurred in 65% of the infections. Montgomery and co-authors (*12*) in 1986 reported that 48% of oral mucositis lesions in a mixed chemotherapy and BMT population cultured positive for HSV and 60% of lesions cultured positive in the BMT group separately. All lesions responded dramatically to acyclovir therapy. They stressed that lesions involved any oral and perioral surface and could not be diagnosed by clinical impression. Greenberg and co-authors (*13*) in 1987 reported that 50% of a group of seropositive leukemia patients treated with chemotherapy developed oral HSV lesions. Of all mucositis lesions, 68% were culture and cytology positive for HSV. They also showed that the more severe mucositis lesions were positive for HSV and that any oral and perioral surface could be involved.

It is important to have a clear understanding of the broad range of clinical presentations for oral HSV lesions in the patient on high-dose cancer chemotherapy. Lesions do occur on the lips, as in patients who are not immunosuppressed, but the lesions are commonly much larger, more painful, and slower to heal. Unlike lesions in otherwise healthy patients, lesions in the chemotherapy patient can involve any intraoral surface, including all surfaces of the tongue, the hard and soft palate, and all mucosal tissues. A blister stage for these lesions is not usually seen, as soft tissue ulceration is the common presenting form. Because of the great variation in the clinical appearance of these lesions, diagnosis by clinical impression alone is very difficult. Laboratory testing should be done to make the diagnosis.

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Table 1. Studies evaluating the incidence of oral HSV infections in patients receiving BMT or cytotoxic chemotherapy[a]

Investigators (ref. No.)	No. of patients	Patient type (No.)	HSV antibody[b] (No. of patients)	Incidence of oral HSV infection (% of patients)	Course of infection [median in days (range)]	Observation period
Meyers et al. (*2*)	141	BMT, allogeneic	76 seropositive 65 seronegative	82% 1.6% (45% total)	Onset: 64% in first 5 wk	120 days
Saral et al.[c] (*4*)	10	BMT (1 syngeneic, 2 autologous, 7 allogeneic)	All seropositive	70%	Onset: 11 (7–17)	80 days
Meyers et al.[c] (*3*)	46	Immunocompromised	>80% seropositive	85%	Viral shedding: 16.8 Crusting: 13.5 No pain: 13.1 Total healing: 20.1	49 days
Wade et al.[c] (*5*)	17	BMT, allogeneic	All seropositive	65%	Viral shedding: 17 Crusting: 14 No pain: 16 Total healing: 28 Second recurrence: 47 (42–62)	49 days
Prentice[c] (*6*)	30	BMT (allogeneic) and chemotherapy	All seropositive	50% of BMT patients, 50% of chemotherapy patients		10–24 mo
Gluckman et al.[c] (*7*)	19	BMT (18 allogeneic, 1 autologous)	10 seropositive 9 seronegative	90% 44% (68% total)		100 days
Hahn et al.[c] (*8*)	30	Immunocompromised	All seropositive	50% of BMT patients, 50% of chemotherapy patients		14 mo
Wade et al. (*9*)	60	BMT, allogeneic	All seropositive	73%	Onset: 7 (4–10) Second recurrence: 66%	33 days

[a] From Montgomery et al. (*12*). Used with permission.

[b] All studies used complement fixation to determine HSV antibody levels, and only titers $\geq$1:8 were considered seropositive.

[c] These studies evaluated the efficacy of acyclovir therapy. The statistics cited here represent the control group. All studies required the presence of oral lesions with positive viral cultures for diagnosis of HSV infection.

Table 2. Studies relating oral mucositis and reactivation of HSV infection in patients receiving BMT or cytotoxic chemotherapy

Investigators (ref. No.)	No. of patients	Patient population (No.)	HSV antibody	Incidence of HSV infection (%)		Median time to onset (days)
Seto et al. (*10*)	30	BMT	Not done	37		18
Barrett (*11*)	70	BMT (12); chemotherapy (22)	Not done	Combined: BMT: Chemotherapy:	40 92 39	Not given
Montgomery et al. (*12*)	29	BMT (15); chemotherapy (15)	Not done	Combined: BMT: Chemotherapy:	48 60 36	Not given
Greenberg et al. (*13*)	26	Leukemia (chemotherapy)	All seropositive	50		Not given

HSV reactivation appears to be a common problem for patients who receive high-dose cancer chemotherapy or BMT. A high percentage of oral mucositis episodes in these patients will have an HSV component. The lesions can involve any oral and perioral soft tissue surface, are associated with severe mucositis, and are difficult to diagnose on clinical grounds alone. Therefore, all mucositis lesions in this patient population should be evaluated by laboratory testing for HSV and treated if found to be positive. The high incidence of HSV infection would also justify consideration of antiviral prophylaxis for patients found to be seropositive prior to chemotherapy.

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Management of Acute Viral Infections

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Oral ulcerations are frequently observed in cancer patients receiving chemotherapy or radiation therapy. Herpes simplex virus is the most common viral pathogen associated with lesions. Reactivation of latent virus is responsible for the vast majority of culture-positive infections. The natural history of this virus has been well studied in selected patient populations. These infections may cause local complications and, if untreated, may not heal for weeks. Reactivation of the virus may occur predictably in patients after bone marrow transplantation or acute leukemia. Recognition that herpes simplex virus is present in oral lesions is of importance because of the availability of safe, effective antiviral therapy. Prospective, randomized, double-blind clinical trials have demonstrated that acyclovir is the most effective agent to treat or prevent herpes simplex virus infections in immunocompromised patients [NCI Monogr 9:107–110, 1990]

The most common viral pathogen associated with oral lesions in immunocompromised cancer patients is herpes simplex virus. This virus has been well studied in some patient populations. However, the true extent of their infection has not been determined because prospective studies have not been performed in large patient populations, such as solid tumor patients receiving chemotherapy or radiation therapy.

The studies evaluating the role of herpes simplex virus in causing infection in immunocompromised patients are important to review because they demonstrate the severity of the lesions that occur and emphasize that atypical oral lesions may in fact be secondary to the virus rather than secondary to some other cause (e.g., chemotherapy). The majority of infections caused by herpes simplex virus occur because of reactivation of latent virus. Primary infections are extremely rare. Therefore, patients can be divided into two distinct groups. Patients who harbor latent herpes simplex virus have antibody against the virus that may be detected in their sera and are seropositive. These patients are at risk for reactivation of the virus with immunosuppression. In contrast, patients without antibody to the virus are seronegative and are unlikely to develop herpes simplex virus infection with immunosuppression. The incidence and severity of herpes simplex infection depend on the intensity of the immunosuppression experienced by the patient. The bone marrow transplantation population offers a group of patients who receive intensive chemotherapy alone or with total-body irradiation for their disease and who have been well studied to determine the incidence and severity of herpes simplex virus infections.

POPULATIONS AT RISK

Studies done by several groups have shown that seropositive bone marrow transplant recipients are at high risk for reactivating herpes simplex virus and developing clinically significant infection after receiving chemotherapy alone or along with total-body irradiation (*1–3*). In the pre-antiviral agent era, 70%–75% of all bone marrow transplant recipients with positive antibody titers to herpes simplex virus in our center developed reactivated infection in the posttransplant period. Other groups have reported a similar incidence of herpes simplex virus infection in their bone marrow transplant population. Most of these infections occurred within the first month after bone marrow transplantation. In our early series, the median time to diagnosis of a culture-positive herpes simplex virus infection was 8 days after bone marrow transplantation or 17 days following the start of chemotherapy. Therefore, the temporal occurrence of these infections was very predictable. These infections were noted to be quite severe, with extensive local oral ulcerations that caused considerable pain and were sites for superinfection with bacteria and fungi. In a small group of patients, respiratory spread of the virus was responsible for development of herpes simplex viral pneumonia, a highly fatal complication in the pre-antiviral agent era (*4*). Lesions were slow to heal, and weeks were required for complete healing to occur. In one study, the median time to healing was 28 days (*5*). The lesions that were noted in many cases appeared atypical and were believed to be secondary to chemotherapy or radiation therapy. In one study there was a positive correlation between the development of mucositis and the presence of herpes simplex virus, emphasizing the atypical presentation of these lesions in this population (*6*).

Another group that has been well studied is acute leukemia patients. Early studies suggested that herpes simplex virus infections were not common in this patient population (*7*). However, our studies in adult patients with acute leukemia receiving intensive chemotherapy indicated that more than 60% of patients with antibody to herpes simplex virus developed culture-positive infection (*1*). The majority of these infections involved the oral cavity, and in many instances confirmation that oral lesions were of viral origin was obtained by culturing samples of suspicious lesions. More recent studies by other investigators have reported a similar incidence of herpes simplex virus infection in acute leukemia patients receiving chemotherapy (*8*). Another feature of these infections is the predictable temporal occurrence of the infection in relation to the administration of chemotherapy. We found that the median time to the development of herpes simplex virus infection in our leukemia patients was 18 days after irradiation or chemother-

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apy. This is very similar to the temporal occurrence of herpes simplex virus infection in our bone marrow transplant recipients, suggesting that the biology of herpes simplex virus reactivation from the latent state is predictably affected by the use of chemotherapy or radiation therapy.

Extensive, prospective studies have not been done as systematically in other patient populations who receive cytotoxic therapy for their disease. In one study, lymphoma patients who were seropositive for herpes simplex virus had a high incidence of reactivation of the virus after chemotherapy (*9*). We and others have observed reactivation of herpes simplex virus in patients receiving chemotherapy for Hodgkin's disease and solid tumors, although these groups have not been prospectively studied. In addition, we have seen predictable reactivation of herpes simplex virus in patients receiving multiple cycles of chemotherapy after each cycle. Clearly, prospective studies are necessary to define the incidence and severity of herpes simplex virus infections in other patient populations.

The studies reported to date suggest that all oral ulcerations in patients treated with chemotherapy or radiation therapy should be considered suspicious for herpes simplex virus. In order to confirm the role of herpes simplex virus as a potential pathogen in oral ulcerations, diagnostic studies should be performed. Viral culture remains the standard for demonstrating herpes simplex virus in suspicious lesions. However, other tests are available that are less sensitive but may demonstrate the presence of the virus in oral lesions. The Tzauck smear, which is easily performed, may demonstrate the presence of the virus in cells obtained from scraping the lesion. Immunological tests are available that detect the presence of herpes simplex virus antigens. These tests offer the promise of providing rapid information to the clinician managing a patient with oral ulcerations. The rationale for demonstrating herpes simplex virus in oral ulcerations is the current availability of safe, effective antiviral therapy.

EARLY ANTIVIRAL AGENTS

Developments in antiviral research have led to the systematic evaluation of compounds designed to inhibit herpes simplex virus replication. The earliest trials of antiviral therapy against herpes simplex virus were based on anecdotal studies that reported success. Two compounds, cytarabine (cytosine arabinoside) and iodoxuridine, were believed to be effective in these anecdotal studies. However, both were found to be ineffective when studied in appropriately controlled prospective clinical trials (*10,11*).

Vidarabine was the first compound to demonstrate efficacy against herpes simplex virus infections in humans. In controlled prospective clinical trials, this agent was shown to be superior to placebo in treatment of herpes simplex virus encephalitis and neonatal herpes simplex virus infection. While studies evaluating this compound in the treatment of mucocutaneous herpes simplex virus infection in immunocompromised patients showed some benefit, the results were not uniformly in favor of the drug (*12*). Patients who received vidarabine had a statistically significant improvement in pain relief and a shorter duration of fever compared to patients who received placebo. However, no statistically significant improvement was observed in several important variables among patients who received vidarabine compared to those who received placebo. Although trends in favor of vidarabine were seen, no statistical significance was noted in cessation of viral shedding, time to new-lesion formation, and earlier time to crusting. In addition, the compound could only be administered intravenously and required hospitalization to achieve these marginal effects.

ACYCLOVIR

The major development in antiviral therapy against herpes simplex virus was the synthesis of acyclovir (*13*). Studies evaluating its mechanism of action suggested that this compound was highly specific in inhibiting herpes simplex virus replication. The compound is activated to a monophosphate by herpes simplex virus thymidine kinase and then to the triphosphate by cellular enzymes. It then inhibits the herpes simplex virus DNA polymerase and terminates viral DNA synthesis. In vitro studies demonstrated that herpes simplex virus replication is inhibited by acyclovir at concentrations that phase I studies demonstrated were easily achieved in humans.

After phase I studies demonstrated that acyclovir was not responsible for any acute life-threatening toxic effects and that the intravenous formulation had a defined pharmacological profile, phase II studies were initiated to evaluate its efficacy against herpes simplex virus in humans.

One of the first clinical trials evaluating acyclovir was conducted in our bone marrow transplantation patients (*14*). Because of the high incidence of herpes simplex virus infections and predictable time to infection, we believed that we could demonstrate the potent antiviral effect of acyclovir in this population. Therefore, we designed a sequential, prospective, placebo-controlled, randomized, double-blind study to evaluate the then-new compound acyclovir. Seropositive bone marrow transplant recipients were randomized to receive intravenous acyclovir at a dose of 250 mg/m^2 every 8 hours or placebo starting 3 days before transplantation and continuing for 18 days. After 20 patients had been enrolled in the study, an interim analysis was performed. The results were dramatic. Seven of 10 placebo recipients developed culture-positive herpes simplex virus infection. In contrast, none of 10 patients who received acyclovir developed such infection ($P = .003$). This study confirmed the efficacy of acyclovir in humans as a potent anti-herpes simplex virus agent.

At the same time we were conducting our trial, a multicenter trial was evaluating acyclovir in the treatment of established herpes simplex virus infections in immunocompromised patients (*15*). This trial was also prospective, placebo controlled, randomized, and double blind. Patients received intravenous acyclovir at a dose of 250 mg/m^2 every 8 hours or placebo. Almost 100 patients were enrolled in this study, which demonstrated a statistically significant benefit to acyclovir recipients in all important clinical variables. The most dramatic effect seen in this trial was the time to cessation of viral shedding in the acyclovir recipients (median, 2.8 days) compared to the placebo controls (median, 16.8 days) ($P < .0002$). This effect translated into a significant decrease in pain, decreased time to crusting of lesions, and decreased time to complete healing.

Two additional formulations of acyclovir, topical and oral, have also been carefully studied in the treatment of established herpes simplex virus infections in immunocompromised patients. Topical acyclovir applied six times per day to lesions showed efficacy compared to placebo controls in a clinical trial

conducted in 63 patients (*16*). Efficacy was greatest in patients with large lesions (greater than 50 mm in diameter), but positive effects were seen in all variables evaluated, including time to healing. Oral acyclovir at a dose of 400 mg five times per day was clearly superior to placebo in the treatment of established herpes simplex virus infection in bone marrow transplant recipients (*17*).

All of the prospective, placebo-controlled, randomized, double-blind studies evaluating the three formulations of acyclovir have shown the drug to be efficacious in the treatment of established herpes simplex virus infection in immunocompromised patients.

Our current recommendations for treatment of established infections are based on the results of these studies. Oral acyclovir is recommended for outpatients. Intravenous acyclovir is recommended for inpatients unless the patient is very compliant and is experiencing no significant symptoms, such as severe oral pain or nausea and vomiting. Topical acyclovir should be reserved for patients whose lesions are external.

The optimal dose for herpes simplex virus infection has not been determined, but in the clinical trials, the intravenous dose was 250 mg/m^2 every 8 hours, the oral dose was 400 mg five times a day, and the topical dose was six applications per day.

ACYCLOVIR AS PROPHYLAXIS

An alternative to treating patients who have established herpes simplex virus infection is the use of acyclovir as prophylaxis. This approach should only be considered for patient groups that show a high incidence of infection that occurs in a predictable time frame. Our study with bone marrow transplant recipients has been confirmed with both intravenous and oral acyclovir (*18–20*). In these studies, as in our original study, acyclovir inhibited herpes simplex virus replication and prevented culture-positive lesions while patients were receiving the drug. Because our studies showed that acute leukemia patients have a high incidence of infection following chemotherapy, we performed a trial of acyclovir prophylaxis in this patient population.

Seropositive adult leukemia patients were randomized to receive intravenous acyclovir or placebo in a prospective, double-blind study. Treatment was initiated on day 4 after chemotherapy. Thirty patients were enrolled in this trial, and 29 were evaluable. Eleven of 15 placebo recipients developed culture-positive herpes simplex virus infection. In contrast, none of 14 patients who received acyclovir developed infection ($P = .0002$) (*21*). This trial demonstrated that herpes simplex virus infections occur frequently in this population, as demonstrated in our original studies, and that acyclovir could prevent reactivation of the virus and culture-positive infection. Other groups have shown similar results for their patients with acute leukemia receiving chemotherapy (*9,18*).

Among seropositive lymphoma patients receiving aggressive chemotherapy, 60% experience reactivation of herpes simplex virus, and these infections can be prevented by using acyclovir, as demonstrated in a study performed in the United Kingdom (*9*).

Based on the results of clinical trials, the use of acyclovir to prevent reactivated herpes simplex virus infections provides an alternative to treatment of established infection. We currently use the agent as prophylaxis in our seropositive bone marrow transplant recipients and in our seropositive leukemia patients. We do not recommend this approach routinely for other patient populations and await further studies to see whether prophylaxis can be expanded to these populations. Only prospective controlled clinical trials will answer this question. To date, several hundred leukemia patients and bone marrow transplant recipients have received prophylaxis, and only a few isolated patients have demonstrated breakthrough of viral replication after this approach.

The appropriate dose and dose schedule for the prophylaxis of herpes simplex virus infection have not been determined. We recently demonstrated that a dose of 125 mg/m^2 given intravenously every 6 hours is equivalent to the higher dose (250 mg/m^2 given every 8 hr) used in the original studies. Other investigators have shown that a dose of 250 mg/m^2 given intravenously every 12 hours or oral acyclovir at 200–400 mg five times a day provides effective prophylaxis (*18,20*).

SIDE EFFECTS AND DEVELOPMENT OF RESISTANCE

Acyclovir has been used therapeutically for years. Side effects attributable to the drug are few. The major toxic effects reported are fortunately rare. Neurotoxicity characterized by tremor, confusion, agitation, hallucinations, and seizures appears to be an idiosyncratic reaction that is reversible within days of discontinuing the drug. Nephrotoxicity may occur, especially at high doses and in patients with underlying renal insufficiency. This toxic effect may be prevented with adequate hydration or resolved by discontinuation of the compound. Other less serious side effects include headache, nausea, vomiting, and rash with oral and intravenous acyclovir and local irritation with topical acyclovir.

A major theoretical problem related to the use of acyclovir in clinical practice is the development of resistance to the agent. Shortly after the introduction of acyclovir into clinical trials, there were isolated reports of acyclovir resistance developing in patients treated with the drug for active herpes simplex virus infection (*22–24*). Recently, a report documented 12 patients with the acquired immunodeficiency syndrome who had acyclovir-resistant virus cultured from lesions that were not responding to acyclovir treatment (*25*). The strains were rigorously investigated, and all were deficient in thymidine kinase activity. In one patient who failed to respond to the acyclovir and who had an acyclovir-resistant strain of herpes simplex virus isolated from a lesion, treatment with foscarnet resulted in healing of lesions (*26*). The potential for the development of resistance has therefore been demonstrated in humans, especially in immunocompromised patients being treated for active infection. One method of minimizing resistance is the use of antiviral therapy as prophylaxis, as was outlined elsewhere (*27*). Clearly this is not practical for all patient populations. The development of new antiviral agents, such as foscarnet, with different mechanisms of action should provide therapeutic alternatives if acyclovir resistance proves to be a major clinical problem in the future.

SUMMARY

Advances in antiviral therapy have led to the availability of safe and effective therapy for herpes simplex virus infections in immunocompromised patients. Acyclovir has been shown in

clinical trials to be the treatment of choice. This agent may be used to prevent infections in selected patient populations. The availability of treatment should alert clinicians to suspect herpes simplex virus as a potential pathogen in all oral lesions encountered in immunocompromised patients. Future studies need to address the potential problem of acyclovir resistance and the development of additional drugs directed at herpes simplex virus.

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Monotherapy for Empirical Management of Febrile Neutropenic Patients

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New fever in a neutropenic patient mandates prompt institution of empirical broad-spectrum antibiotics. Traditional empirical regimens have relied on combinations that include an aminoglycoside. However, certain classes of newer antibiotics (e.g., third-generation cephalosporins, carbapenems, quinolones) include agents with a broad spectrum and high bactericidal activity that may provide therapeutic alternatives to combination regimens. We previously compared empirical monotherapy with ceftazidime to a combination regimen of cephalothin, gentamicin, and carbenicillin and found the regimens comparable with respect to percentage with success (survival without change of initial regimen; 62% vs 67%), success with modification (survival with additional antibiotics; 33% vs 29%) and failure (death; 5% vs 4%). Imipenem has a broader in vitro spectrum of activity than ceftazidime, particularly against gram-positive organisms and anaerobes, raising the possibility of equivalent or even improved efficacy as monotherapy. Accordingly, we are prospectively randomizing febrile, neutropenic patients to either empirical ceftazidime or imipenem therapy. Imipenem appears to be comparable to ceftazidime in this ongoing study but has not resulted in fewer modifications or secondary infections. Studies assessing the role of quinolones in the management of neutropenic patients are under way. [NCI Monogr 9:111–116, 1990]

The polymorphonucleocyte is the single most important component of host defense that functions to protect against invasive bacterial and fungal pathogens. Not surprisingly, the development of granulocytopenia in the cancer patient (usually resulting from cytotoxic chemotherapy or radiotherapy) presents the most significant risk for development of subsequent infection. The risk of developing serious infections is related to both the absolute granulocyte count and the duration of granulocytopenia (*1*). With granulocyte counts above 1,000/μL, the risk of infection is small. However, as the count falls below this value, and more notably when it falls below 500/μL, the risk increases precipitously. Patients who have "profound" granulocytopenia, with counts less than 100/μL, appear to represent a subset at particularly high risk of infection. For practical purposes, granulocytopenia is usually defined as a cell count of ≤500 polymorphonucleocytes and band forms per μL. In addition, the longer the duration of granulocytopenia, the greater the chance of developing significant infection.

Although granulocytopenia is the most important and the most easily measurable risk factor for infection in this population, other abnormalities of host defense are frequently present, often as a result of both the underlying malignant disease and its therapy. Examples include breakdown in physical defense barriers (e.g., from insertion of indwelling intravenous catheters or as a result of other disruptions of mucosa and skin), abnormalities in other infection-fighting systems (e.g., immunoglobulin abnormalities seen in certain hematological malignancies or defects in cell-mediated immunity), and changes in patterns of microbial colonization. Disruption of the oral mucosa may be an important antecedent event to both colonization with and invasion by potentially pathogenic bacteria. A number of factors can potentially contribute to oral mucosal disruption, including chemotherapy and radiotherapy, invasion by tumor, and a variety of nonbacterial infectious processes.

It has become well accepted that the onset of fever in a neutropenic patient requires the prompt initiation of empirical antimicrobial therapy. The main goal of empirical antibiotics is to protect against the early morbidity and mortality associated with untreated bacterial infections in the neutropenic population. However, empirical regimens cannot realistically be designed to cover every potential bacterial pathogen. Likewise, no regimen is capable of completely eliminating the risk of subsequent infections in persistently neutropenic patients.

Qualities considered essential for empirical regimens are (*a*) a broad spectrum of activity, encompassing gram-positive and gram-negative organisms (including *Pseudomonas aeruginosa*), (*b*) the use of bactericidal drugs that achieve bactericidal levels in both serum and tissue, (*c*) efficacy against virulent organisms even in the absence of neutrophils, and (*d*) an acceptable toxicity profile. Historically, in order to accomplish these goals, it has been necessary to use combinations of antibiotics. Most empirical combination-antibiotic regimens have consisted of an aminoglycoside at "the core," usually in combination with an extended-spectrum or antipseudomonal beta-lactam antibiotic, and often including some additional gram-positive coverage provided by a first-generation cephalosporin, antistaphylococcal penicillin, or vancomycin (table 1) (*2*).

Given the fact that aminoglycoside-based combination regimens have provided a time-honored profile of effective empirical coverage, one might appropriately ask if there are any valid reasons to reconsider their use in this population. Indeed, a number of factors support the search for alternative regimens:

Change in the pattern of bacterial isolates. While gram-negative organisms are still important pathogens requiring appropriate antibiotic coverage, many centers are witnessing the reemergence of gram-positive organisms as the most frequently encountered isolate.

Increasing aminoglycoside resistance. With the increased use of aminoglycosides, some institutions are encountering a concomitant rise in aminoglycoside-resistant gram-negative organisms.

Concerns about toxic effects. As potentially toxic agents are increasingly used in the management of many underlying malignancies, valid concerns arise about additive toxic effects (particularly nephrotoxicity) of the aminoglycosides. Examples

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Table 1. Aminoglycoside-based combination regimens

Aminoglycoside	Antipseudomonal beta-lactam	Additional anti-gram-positive
Gentamicin Tobramycin Amikacin Netilmicin	Extended-spectrum penicillin (carbenicillin, ticarcillin, azlocillin, mezlocillin, piperacillin) or third-generation cephalosporin (ceftazidime, cefoperazone) or monobactam (aztreonam)	Isoxozolyl-penicillin (nafcillin, oxacillin) or first-generation cephalosporin (cephalothin, cephazolin) or glycopeptide (vancomycin, teicoplanin)

include the potential for added nephrotoxicity with platinum-based compounds and cyclosporin.

Changes in the spectrum of neutropenic patients. When many of the initial empirical regimens were developed, they were directed mainly to patients with hematological malignancies that were treated with earlier-developed cytotoxic regimens. Subsequently, refinements in the delivery of cytotoxic therapy and supportive care, coupled with the development of novel antineoplastic strategies, have resulted in a more heterogeneous population at risk for infection. The clinician now frequently encounters neutropenic patients with solid tumors as well as hematological malignancies. This often results in significant variations in the degree and duration of neutropenia, as well as in additional risk factors.

Concerns about cost. The cost of antibiotic regimens is an increasingly important and relevant issue. The cost of combination regimens may be relatively high, not only because of the costs of the antibiotics per se, but also because of additional factors such as staff time for drug preparation, cost of apparatus for intravenous administration, and monitoring of antibiotic levels (e.g., for aminoglycosides and vancomycin). Most importantly, certain newer antibiotic developments have provided us with alternatives to the more traditional, aminoglycoside-based combination regimens (*3,4*). At the National Cancer Institute, United States, we have been particularly interested in the concept of single-agent empirical therapy, or monotherapy.

At present, three classes of currently available antibiotics include potential candidates for monotherapy—the third-generation cephalosporins, the carbapenems (of which imipenem is the prototype), and the quinolones (*4*). At the National Cancer Institute, we have developed a series of clinical studies designed to assess agents from each of these classes in this setting. The monobactams (of which aztreonam is the prototype) are another relatively new class of antibiotics being evaluted for efficacy in neutropenic patients. This discussion will focus on the potential clinical utility of these agents for empirical therapy in febrile granulocytopenic cancer patients.

THE THIRD-GENERATION CEPHALOSPORINS

While many third-generation cephalosporins are available, most are not appropriate for single-agent empirical therapy, primarily because of a lack of activity against *Pseudomonas aeruginosa* (*5,6*). Of the third-generation cephalosporins currently available in the United States, only cefoperazone and ceftazidime have any significant activity against *P. aeruginosa*, and of these, ceftazidime's activity is greater.

The first trial of monotherapy conducted at the National Cancer Institute was designed to determine whether a single broad-spectrum beta-lactam could be as effective as a standard combination regimen for initial empirical therapy (*7*). In that study, patients with fever (one oral temperature ≥ 38.5 °C or three temperatures ≥ 38 °C in a 24-hr period) and granulocytopenia (≤ 500 granulocytes and band forms per μL) underwent a standard initial evaluation and then were randomized to receive either a combination regimen consisting of cephalothin, gentamicin, and carbenicillin (KGC) or ceftazidime alone.

In our judgment, the most important objective with respect to the effectiveness of an empirical regimen is its impact on survival of the patient through the neutropenic episode. Moreover, it is during the initial 72 hours, before initial culture results are available, that the therapy is truly empirical. Accordingly, in this trial, we evaluated patients for success of therapy (alive vs dead) at 72 hours after entry in the study and also for the remainder of the neutropenic episode. In addition, we grouped patients according to whether their initial workup (including cultures) revealed a documented infection or fever of undetermined origin.

The results, based on 550 patient episodes, indicate that monotherapy with ceftazidime compares favorably with the combination regimen. Survival at both the early and later evaluation time points was the same for each group. The overall results also show comparable efficacy of the two regimens (table 2). Approximately two-thirds of the episodes in both groups were successfully treated for the duration of the granu-

Table 2. Outcome of 550 febrile neutropenic episodes randomized to monotherapy or combination antibiotic therapy[a]

Regimen	Total No. of episodes	No. (%) of episodes		
		Success without modification[b]	Success with modification[c]	Failure[d]
Monotherapy (ceftazidime)	282	175 (62)	93 (33)	14 (5)
Combination therapy (KGC)[e]	268	180 (67)	78 (29)	11 (4)

[a] From Pizzo et al. (*7*).
[b] Successful treatment not requiring any addition to or change in the initial antibiotic regimen.
[c] Successful treatment requiring some additions to or changes in the initial antibiotic regimen.
[d] Death due to infection.
[e] KGC = cephalothin, gentamicin, and carbenicillin.

locytopenia without requiring any changes in the initial regimen. Another one-third of the episodes required some change or modification (such as addition of an antibacterial, antifungal, or antiviral drug). In the neutropenic patient, modifications of the initial empirical regimen may be required in a number of clinical settings in order to ensure a successful outcome (table 3). Finally, an equally low number in both randomization groups (about 5%) died of infection. None of the deaths were attributable to a specific deficiency in one regimen that was not present in the other (i.e., an organism sensitive to one regimen but resistant to the other). In addition, the average time to initial defervescence was equivalent for those receiving monotherapy and for those treated with combination antibiotics.

Two subgroups of patients were identified in this study that appeared to require more frequent modifications of the initial regimen in order to achieve a successful outcome: those presenting with a documented source of infection to account for the initial fever, and those having relatively protracted periods of granulocytopenia (≥1 wk). Importantly, however, the need for modification in these subgroups was identical regardless of whether the patient was treated initially with monotherapy or with combination therapy. In this study, these modifications were not considered a failure of the primary regimen per se, but instead were reflective of the limitations of virtually any antibiotic in treating patients who are at particularly high risk for development of secondary infections.

Several authorities have raised concerns about the use of ceftazidime as a single agent for fever and neutropenia. These have included the lack of synergy against documented gram-negative infection, lack of activity against certain gram-positive isolates, poor antianaerobe activity, and the potential for development of resistance (*8–14*). Some of these concerns are purely theoretical, while others are based on unique experiences limited to specific centers.

One issue that has been the subject of continued debate is whether vancomycin should be included routinely in initial empirical regimens, particularly if single-agent therapy is used. Supporting the argument for routine use of vancomycin is the observation that gram-positive organisms have been increasing in incidence and now constitute the majority of isolates at many centers. Many of these (such as enterococci and the coagulase-negative staphylococci) are inadequately covered by many empirical regimens. Conversely, it has been argued that since many of these organisms are of relatively low virulence and are often inhibited by the antibiotics (even "suboptimal" antibiotics), vancomycin may be safely withheld until the gram-positive isolate has been identified microbiologically.

One recent study randomized patients between a vancomycin- and a non-vancomycin-containing regimen and showed that the incidence of secondary gram-positive infections was reduced in the vancomycin group (*9*). There also appeared to be less of an amphotericin B "requirement" in the group that received vancomycin as part of the initial regimen. However, there was no difference in morbidity related to gram-positive infections between the two groups, and all of the gram-positive infections in the non-vancomycin group were successfully treated with vancomycin when the organism was identified and reported by the microbiology laboratory.

A retrospective analysis from the National Cancer Institute, in contrast, indicated that there was no excess morbidity associated with delaying the institution of vancomycin therapy by waiting for either a microbiological or clinical indication for its use (*15*). One hundred percent of the primary gram-positive isolates (from cultures obtained prior to empirical therapy) and 82% of the secondary gram-positive isolates (from cultures obtained after institution of antibiotics) were treated successfully with this pathogen-directed approach. Of the three patients with secondary gram-positive isolates who were scored as failures, only one represented a true microbiological failure, with blood cultures persistently positive for *Enterococcus faecalis* after 2 days of vancomycin therapy. This patient was treated successfully following a change to ampicillin and gentamicin. The other two patients died of noninfectious causes while receiving vancomycin and, since they did not represent true successes, were scored conservatively as failures. There was a greater proportion of secondary gram-positive infections in the group initially receiving monotherapy (ceftazidime) than in the combination-therapy group (16 of 282 patients compared with six of 268; $P_2 = .04$, chi-square test), but all of these patients were treated successfully by subsequent addition of vancomycin.

Another study randomizing patients between a vancomycin- and non-vancomycin-containing regimen also demonstrated more gram-positive infections in the latter group, but in eight of

Table 3. Possible modifications of initial empirical therapy

Clinical event	Appropriate modification(s)
Breakthrough bacteremia	If gram-positive isolate (e.g., *Staphylococcus epidermidis*), add vancomycin; if gram-negative isolate (i.e., presumably resistant), switch to new regimen
Catheter-associated infection	Add vancomycin for resistant gram-positive organisms
Severe oral mucositis or necrotizing gingivitis	Add specific antianaerobe agent (e.g., clindamycin or metronidazole)
Esophagitis	Trial of oral clotrimazole or iv amphotericin B and/or acyclovir
Pneumonitis—diffuse or interstitial	Trial of trimethoprim-sulfamethoxazole and erythromycin (plus broad-spectrum antibiotics if neutropenia present)
Pneumonitis—new infiltrate in a granulocytopenic patient receiving antibiotics	Granulocyte count rising—watch and wait; granulocytopenic—biopsy, lavage, or empirical therapy
Perianal tenderness/infection	Add antianaerobe agent
Persistent fever and granulocytopenia	Empirical amphotericin B

nine of these patients there was no excess morbidity reported due to delaying institution of the vancomycin until after the organism was recovered (*16*). Interestingly, the conclusion drawn from this study was that vancomycin should be used routinely in empirical regimens. The weight of the recommendations rested on a single case of fatal gram-positive sepsis that occurred in a patient not receiving vancomycin, although the organism was susceptible to the antibiotic regimen that the patient was receiving at the time (ticarcillin-clavulanate plus amikacin). Also, this organism was only cleared after institution of therapy with another beta-lactam (cefotaxime) in combination with vancomycin.

Clearly, an important factor to be considered in the selection of components for empirical regimens is the sensitivity pattern of organisms encountered at a given institution. For example, while vancomycin may not be a necessary component of empirical regimens at most centers, its routine use is clearly appropriate at institutions with a high incidence of methicillin-resistant *Staphylococcus aureus* infections.

THE CARBAPENEMS

Imipenem is a relatively new agent and the prototypic member of the carbapenem class of antibiotics. It is provided in fixed combination with cilastatin, an inhibitor of renal dehydropeptidase, an enzyme that rapidly degrades imipenem. Its spectrum of activity compared with that of ceftazidime is reviewed in table 4. Of note is that in addition to good in vitro activity against the important aerobic gram-negative pathogens, imipenem has improved activity against gram-positive organisms (including most enterococci) and also against most of the clinically important anaerobic bacteria (including *Bacillus fragilis* and *Clostridium* spp.).

With respect to the potential use of imipenem as a single agent for empirical therapy, two questions are relevant. First, will it be as effective as ceftazidime for empirical monotherapy? Second (and perhaps more importantly), will its broadened activity translate into improved clinical efficacy?

An initial small, nonrandomized study suggested that imipenem may be useful and effective as monotherapy (*17*). Early results of two randomized studies appear to corroborate its efficacy in this setting (one comparing it to an aminoglycoside-containing combination, and another, being performed at the National Cancer Institute, comparing it to monotherapy with ceftazidime) (*18,19*). Preliminary results of the National Cancer Institute trial are presented in table 5. Interestingly, neither of these studies appears to demonstrate superior efficacy. Three potential drawbacks to the use of imipenem are a relatively high incidence of development of resistant *P. aeruginosa*, its potential to decrease the seizure threshold in patients with central nervous system pathology, and its potential to cause significant nausea and vomiting in some patients. In the ongoing trial, approximately one-third of the patients receiving imipenem report significant nausea, and about one-third of the patients experiencing nausea have required discontinuation of the drug. In contrast, only about 2% of patients receiving ceftazidime report associated nausea, with none requiring discontinuation.

THE QUINOLONES

The fluoroquinolones are agents with a broad spectrum of activity that encompasses the majority of pathogens encountered in neutropenic patients. Their activity against most aerobic gram-negative organisms (including *P. aeruginosa*) and staphylococci (including methicillin-resistant strains) is excellent. However, they have only moderate activity against many streptococci and show no activity against any of the clinically important anaerobes.

The appropriate role for the quinolones in the neutropenic patient has yet to be defined. Because of their relatively poor activity against certain gram-positive organisms, they should probably not be used for empirical single-agent therapy. They may, however, be useful for completion of therapy in patients who initially respond to intravenous antibiotics and who have had either a fever of undetermined origin or a susceptible organism isolated. At the National Cancer Institute, we are currently randomizing such patients (if they are still neutropenic after 3 to 7 days of intravenous antibiotics) to either continue the intravenous therapy or switch to oral ciprofloxacin. Clearly, the ability to identify low-risk patients who could be switched to oral therapy might be of practical benefit.

Another potential use for the quinolones that has received recent attention is for oral prophylaxis of bacterial infections in patients with prolonged neutropenia. Thus far, the published data suggest that the incidence of gram-negative infections in patients receiving quinolones may be decreased. Despite this, however, none of the studies has shown a decrease in infection-related death, and two have shown some increase in gram-positive infections (*20–23*). At present, the clinical usefulness of the quinolones as prophylactic agents has not been definitively established. Importantly, their overuse may lead to significant quinolone resistance, vitiating all beneficial potential.

AZTREONAM

Aztreonam is a relatively new, synthetic beta-lactam antibiotic of the monobactam class. Although it shares certain structural features with other beta-lactams, its monocyclic structure provides a unique microbiological spectrum and clin-

Table 4. Spectrum of antibacterial activity

Coverage	Ceftazidime	Imipenem
Effective in vitro		
Gram-negative aerobes	Good (including *P. aeruginosa*)	Good (including *P. aeruginosa*)
Gram-positive bacteria	Moderate (excluding enterococci)	Good (including enterococci)
Anaerobes	No	Good
Deficient	Methicillin-resistant staphylococci, *Pseudomonas maltophilia, Pseudomonas cepacia,* anaerobes, *Listeria* spp.	Methicillin-resistant staphylococci, *P. maltophilia, P. cepacia*

Table 5. Outcome of 126 febrile neutropenic episodes randomized to monotherapy with ceftazidime or imiprenem[a]

Regimen	Total No. of episodes	No. (%) of episodes		
		Success without modification[b]	Success with modification[c]	Failure[d]
Ceftazidime	65	42	54	5
Imipenem	61	52	44	3

[a]From Falloon et al. (*19*).
[b]Successful treatment not requiring any addition to or change in the initial antibiotic regimen.
[c]Successful treatment requiring some additions to or changes in the initial antibiotic regimen.
[d]Death due to infection.

ical profile. It can only be used intravenously and has a pharmacologic and toxicity profile similar to those of other beta-lactam antibiotics.

Aztreonam has a relatively narrow, highly specific spectrum of activity directed against aerobic gram-negative bacteria. Susceptible organisms include most enteric gram-negative rods as well as *P. aeruginosa*. In contrast, aztreonam has no significant activity against any of the clinically important gram-positive aerobic organisms or against anaerobes. A number of studies in nonneutropenic patients have shown aztreonam to be effective for treating serious gram-negative infections. On the other hand, there is very limited data with respect to its use in the neutropenic population. One early study suggests that it may provide effective empirical coverage for febrile neutropenic patients when combined with vancomycin [in order to provide gram-positive coverage (*24*)]. More data are needed, however, to clarify its utility for single-agent gram-negative coverage in this population. Until this information is available, addition of an aminoglycoside is warranted if aztreonam is selected for use.

A particularly useful feature of aztreonam is its apparent lack of cross-reactivity with the other beta-lactams in patients who have penicillin or beta-lactam allergies (*25*). It is in this setting that it may be most useful—specifically for the patient with a significant allergy to beta-lactams for whom therapy with an antipseudomonal beta-lactam antibiotic is still desirable or required. An appropriate empirical regimen for this group of patients might be a combination of vancomycin, aztreonam, and an aminoglycoside.

CONCLUSION

It is well established that the onset of fever in the granulocytopenic patient mandates the expeditious institution of empirical antibiotic therapy. Traditionally, combination regimens have been used to achieve the desired properties of empirical therapy. They have usually consisted of an aminoglycoside combined with an antipseudomonal penicillin and have often included an anti-gram-positive organism beta-lactam. However, the development of newer broad-spectrum antibiotics that can achieve high bactericidal concentrations has provided potential alternatives to the traditional combination regimens. These include non-aminoglycoside-containing combinations and certain agents used alone. With respect to monotherapy, the third-generation cephalosporins and the carbapenems have been studied most extensively, each offering agents of potential clinical usefulness. In addition, studies are under way to help determine the most appropriate role for the fluoroquinolones in neutropenic patients. Finally, the monobactams provide the clinician with an antipseudomonal agent that can be safely used in beta-lactam-allergic patients. Again, it should be emphasized that there are a variety of appropriate options for empirical antibiotic management and that there is no single best approach. The selection of a specific regimen should depend on many factors, including institutional sensitivity patterns, individual and institutional experience, and clinical parameters.

In terms of future study related to oral pathology and neutropenic patients, a number of questions need to be addressed. Importantly, the role of mucosal damage in predisposing patients to subsequent bacterial and fungal infections should be better defined. If the patterns and mechanism of colonization by pathogenic organisms can be determined, this information could have potential implications for both prevention of infection and individualization of empirical therapy.

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Combination and Single-Agent Empirical Antibacterial Therapy for Febrile Cancer Patients With Neutropenia and Mucositis[1]

Jerry L. Shenep[2,*]

The role of mucositis in infectious complications in the patient with cancer is poorly understood. Consequently, neither the presence nor the severity of mucositis is routinely considered in the selection of specific antibacterial agents for the initial empirical therapy of the febrile cancer patient. In a study of children receiving remission induction chemotherapy for acute nonlymphocytic leukemia, the number of febrile days correlated more closely with the degree of mucositis than with the number of days of neutropenia. Oral mucositis appears to predispose cancer patients to systemic infections with alpha-hemolytic streptococci, *Capnocytophaga*, and *Candida* species. Overall, studies of single-drug versus combination therapy for the initial empirical therapy of febrile, neutropenic cancer patients indicate that monotherapy approaches the efficacy of combination therapy, although combination therapy may be preferred for certain cohorts of cancer patients. A concern that is closely related to the issue of combination therapy versus monotherapy is the need for vancomycin in the initial empirical regimen. Vancomycin appears to be the consensus drug of choice for patients with known gram-positive bacterial infections pending antibiotic susceptibility testing; however, there is disagreement as to whether the increased activity of vancomycin against gram-positive bacteria outweighs its expense and potential toxicity for inclusion in the initial empirical regimen. There is an explicit need for continued support of basic and clinical research to address these concerns. [NCI Monogr 9:117–122, 1990]

Infection was recognized as a major fatal complication of cytotoxic antineoplastic chemotherapy soon after its use became widespread (*1*). In 1966, Bodey and colleagues (*2*) originally demonstrated a quantitative relationship between the degree of neutropenia and the incidence of infections in patients with leukemia. Subsequently, Schimpff and colleagues (*3*) asserted that empirical therapy of neutropenic cancer patients was needed because half of the patients with *Pseudomonas* bacteremia died within 72 hours of the initial positive blood culture. These investigators (*3*) reported that the incidence of fatal infection in febrile neutropenic cancer patients was reduced (versus historical controls) through use of empirical combination therapy with gentamicin and carbenicillin. Empirical antibacterial therapy of febrile, neutropenic patients has since gained broad acceptance.

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ROLE OF MUCOSITIS IN SYSTEMIC INFECTION

Neutropenia is generally regarded as the primary risk factor for systemic infection in the cancer patient. However, in a study of children receiving remission induction chemotherapy for acute nonlymphocytic leukemia (*4*), the number of days with fever during the first 10 weeks of therapy correlated more closely with the severity of either oral mucositis or gastrointestinal mucositis than with the duration of neutropenia (P = .016, .003, and .14, respectively; fig. 1). There are several reasons to account for the emphasis on neutropenia over mucositis as a risk factor for infection in the cancer patient. First, with current chemotherapy protocols, severe mucositis is almost always accompanied by bone marrow suppression and neutropenia. Thus, although severe mucositis may be a significant contributing factor, systemic infection can be attributed to neutropenia in most cases, precluding further scrutiny of risk factors. Second, unlike mucositis, which is poorly defined and largely invisible, neutropenia is readily quantitated. Third, as a consequence of the foregoing, relatively little has been published pertaining to the relationship between mucositis and the risk of systemic infection in the cancer patient.

Neutropenic cancer patients are generally at risk for both gram-negative and gram-positive bacterial infections. Recent reports indicate a shift to predominance of gram-positive bacterial infections at some institutions (*5–7*), but the role of mucositis, if any, in this changing spectrum of infections remains largely unexplored. Patients with oral mucositis are especially at risk for infection with alpha-hemolytic streptococci (*8,9*) and, less commonly, *Capnocytophaga* species (*10,11*). In addition, there is limited evidence that oral mucositis predisposes patients to systemic candidiasis (*12*).

INITIAL SELECTION OF A REGIMEN

There is a consensus that neutropenic cancer patients with new onset of fever require immediate parenteral therapy with broad-spectrum antibiotics at maximum doses. Selection of a specific antibacterial regimen for use in empirical therapy of the febrile patient with mucositis and neutropenia should reflect the relative risks of specific pathogens, the expected antibacterial susceptibilities of important pathogens, and the toxic effects of the specific antibacterial drugs. The possibility of inducing resistant organisms and the cost of specific regimens must also be considered.

Because of the wide range of potential pathogens in the febrile, neutropenic cancer patient, empirical antibacterial therapy has traditionally consisted of a combination of two or three drugs. Such combinations theoretically broaden coverage, provide synergistic action against certain pathogens, and reduce the likelihood of emergence of resistant organisms. On the other hand, combination therapy could increase the likelihood of

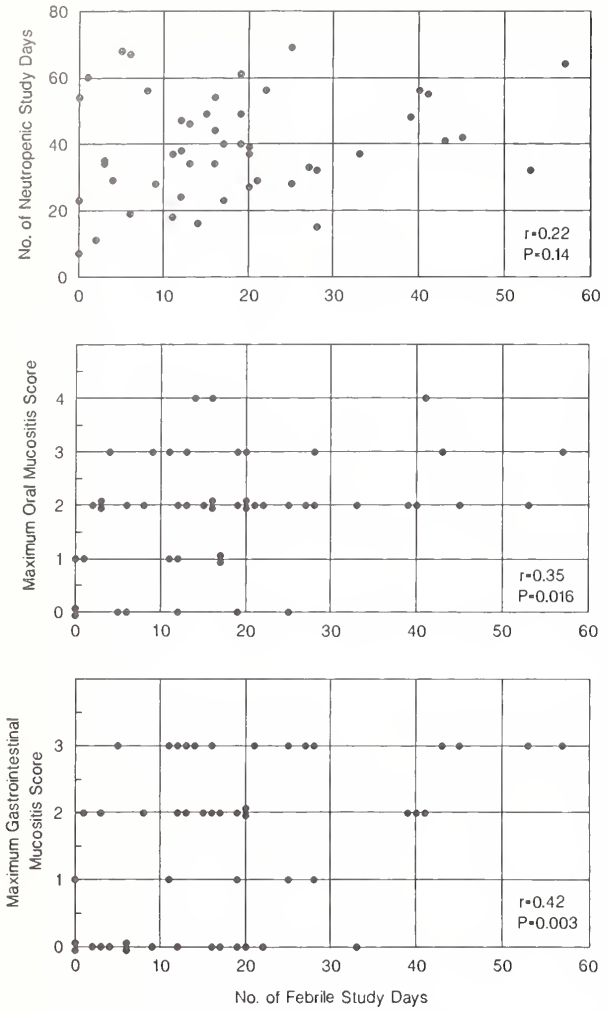

FIGURE 1. Correlation of number of febrile days with number of neutropenic days (top), maximum oral mucositis score (middle), and maximum gastrointestinal mucositis score (bottom). Data are for 48 children with newly diagnosed acute nonlymphocytic leukemia studied for the first 10 weeks of remission induction therapy (*4*). Subjects were randomized to receive either oral sucralfate or placebo, but because there was no significant difference between study groups in these scores, data were pooled for this analysis. Number of febrile study days correlated more closely with degree of mucositis than with number of days of neutropenia. Scale for oral mucositis: 0, normal; 1, erythema; 2, mild ulceration; 3, moderate ulceration; 4, severe ulceration. Scale for gastrointestinal mucositis: 0, less than three stools per day; 1, three to five liquid stools per day; 2, more than five liquid stools per day; 3, bloody diarrhea.

toxicity and is costly in terms of both the expense of multiple drugs and the expense for personnel time to prepare and administer drug combinations. The advent of single drugs with broad antibacterial activity, in particular the third-generation cephalosporins and carbapenems, has encouraged clinical trials comparing the efficacy of single agents (monotherapy) and combination therapy for empirical treatment of the febrile, neutropenic patient (*13–30*) (table 1). These studies provide the only data with which to evaluate objectively the alleged advantages of combination therapy versus monotherapy.

Efficacy

As can be seen in table 1, the majority of studies do not show any significant differences in the outcome of patients randomized to receive monotherapy or combination therapy. It should be noted that the power of most of these studies to detect differences in treatment outcome is limited by small sample sizes. Nevertheless, Pizzo and colleagues (*16*) found no significant difference in the final outcome of over 500 patients randomized to receive ceftazidime versus cephalothin, gentamicin, and carbenicillin. Many patients in that study did, however, require modification of their initial regimen. These patients, if their subsequent courses were satisfactory, were considered successes "with modification," a concept that is somewhat controversial (*31*).

In three studies, patients fared better when treated with combination therapy than with monotherapy (*14,17,22*). In the largest of these studies, the European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group randomized over 500 patients to receive ceftazidime plus 3 days of amikacin therapy (considered monotherapy for purposes of this analysis) or ceftazidime plus 9 days of amikacin therapy (combination therapy) (*14*). Patients receiving combination therapy had better response rates than patients treated with monotherapy ($P = .002$). In a study that was partially randomized and partially sequential, Kramer and colleagues (*17*) found that patients who were treated with ceftazidime plus vancomycin had a lower death rate than patients treated with ceftazidime alone ($P < .05$). Fainstein and colleagues (*22*) reported that cancer patients with pneumonias responded better to the combination of ceftazidime and tobramycin than to ceftazidime alone, but the result was valid only for nonneutropenic patients ($P = .04$).

In one study, patients receiving ceftazidime had more gram-positive but fewer gram-negative breakthrough bacteremias than patients receiving cephalothin, carbenicillin, and gentamicin (*23*). De Pauw and colleagues (*20*) reported a higher response rate to ceftazidime monotherapy than to cefotaxime plus gentamicin ($P < .05$), the only published report that shows a significantly better overall response to monotherapy.

In summary, these trials collectively indicate that ceftazidime monotherapy is generally as efficacious as combination therapy. Nevertheless, it appears that the addition of amikacin (*14*) or vancomycin (*17*) to ceftazidime can improve the outcome (reduced morbidity) of at least certain cohorts of patients treated empirically.

Synergy

One of the theoretical advantages of combination therapy is the potential for synergistic action of antibiotics against specific pathogens. Antibiotic synergy results in greater serum bactericidal activity than can be achieved in the absence of synergy (*32–35*). In addition, limited data indicate that synergistic antibiotic combinations are more effective clinically than combinations in which the pathogen is sensitive individually to each of the component antibiotics, but in which no antibiotic synergy is present. Most notably, de Jongh and colleagues (*36*) reported

Table 1. Clinical trials comparing monotherapy and combination therapy in the empirical treatment of neutropenic patients with fever

Reference No.	Monotherapy	Combination therapy	No. of courses (monotherapy/ combination)	Study design	Outcome
(*13*)	Ceftazidime	Cephalothin, carbenicillin, gentamicin; ceftazidime, vancomycin	55/105; 46	Randomized	No difference
(*14*)	Ceftazidime plus 3 days of amikacin	Ceftazidime plus 9 days of amikacin	290/290	Randomized	Higher response rate with combination ($P = .002$)
(*15*)	Ceftazidime	Ceftazidime, cephalothin	48/42	Randomized	No difference
(*16*)	Ceftazidime	Cephalothin, gentamicin, carbenicillin	282/268	Randomized	No difference
(*17*)	Ceftazidime	Cephalothin, gentamicin, carbenicillin; ceftazidime, vancomycin	21/37; 37	Randomized (partially historically controlled)	Lower death rate with ceftazidime + vancomycin ($P < .05$)
(*18*)	Ceftazidime	Ceftazidime, flucloxacillin	51/49	Randomized	No difference
(*19*)	Ceftazidime	Piperacillin, netilmicin, cefotaxime	33/32	Randomized	No difference
(*20*)	Ceftazidime	Cefotaxime, gentamicin	42/45	Randomized	Higher response rate with monotherapy ($P < .05$)
(*21*)	Ceftazidime	Tobramycin, ticarcillin	54/70	Sequential	No difference
(*22*)	Ceftazidime	Ceftazidime, tobramycin	136/139	Randomized	Pneumonias responded better to combination in nonneutropenic patients
(*23*)	Ceftazidime	Cephalothin, carbenicillin, gentamicin	21/23	Randomized [subset of ref (*17*)]	More gram-positive and fewer gram-negative breakthrough bacteremias with monotherapy
(*24*)	Ceftazidime	Azlocillin, tobramycin	26/24	Randomized	No difference
(*25*)	Cefoperazone	Cefoperazone, amikacin	25/24	Randomized	No difference
(*26*)	Cefotaxime	Ampicillin, methicillin, netilmicin	30/31	Randomized	No difference
(*27*)	Moxalactam	Nafcillin, tobramycin	53/55	Randomized	Increased incidence of nephrotoxicity and rashes with combination
(*28*)	Imipenem	Cefoperazone, piperacillin; ceftazidime, piperacillin	29/29; 27	Randomized	Increased incidence of seizures with imipenem
(*29*)	Imipenem	Cefoperazone, mezlocillin	46/42	Randomized	Increased incidence of nausea with imipenem
(*30*)	Piperacillin	Ticarcillin, gentamicin	26/24	Randomized	Fewer adverse effects with monotherapy

that seven of 11 (64%) patients responded to synergistic combinations of antibiotics, but none of six patients responded to nonsynergistic combinations ($P = .01$), although the pathogen was susceptible individually to each of the component drugs.

Highly active drugs such as ceftazidime can often provide greater serum bactericidal activity against selected gram-negative bacterial pathogens than can be provided by conventional synergistic combinations of aminoglycosides and beta-lactams (*37*). In these circumstances, synergistic antibiotic combinations may not offer any advantage, except perhaps in preventing the emergence of antibiotic-resistant pathogens, as discussed below. Moreover, combination therapy can result in antagonism (*38*).

Prevention of Emergence of Resistant Organisms

Synergistic combinations of antibiotics are thought to help prevent the emergence of resistant organisms (*34*). In support of this tenet, resistant strains emerged more often in neutropenic rats treated with moxalactam or amikacin monotherapy than in rats treated with moxalactam plus amikacin (*39*). There are very few clinical data on the emergence of resistant strains in relation to combination therapy versus monotherapy. In a small study, resistant organisms emerged in six of 26 patients receiving piperacillin alone compared to only two of 24 patients receiving ticarcillin plus gentamicin (*30*). However, this result is not statistically significant ($P = .25$, Fisher's exact test, two tailed).

Toxicity

Combination therapy is often assumed to be more toxic than monotherapy, but the converse may be true depending on the relative toxicity of the specific single agents. Thus, the combination of nafcillin and tobramycin was associated with an increased incidence of nephrotoxicity and rashes compared to moxalactam therapy (*27*), but imipenem produced more seizures and nausea than combination therapy (*28,29*). In general, the relative lack of toxicity associated with combination therapy compared to therapy with a third-generation cephalosporin is noteworthy (table 1).

Cost

Monotherapy may provide substantial monetary savings over combination therapy during the course of empirical therapy for fever and neutropenia (table 2). Moreover, with monotherapy, even greater savings may result from a reduction in the use of intravenous infusion sets and personnel time required to prepare and administer therapy. However, these potential savings may be lost if monotherapy is inordinately expensive or results in prolonged hospitalization or increased use of antifungal therapy (*6*).

ROLE OF VANCOMYCIN

A concern that is closely related to the issue of combination therapy versus monotherapy is the need for vancomycin in the initial empirical regimen for febrile, neutropenic patients. Several clinical trials have addressed this concern (*6,13,17,40–43*) (table 3). There appears to be a consensus that for patients with known gram-positive bacterial infections, vancomycin is the drug of choice pending antibiotic susceptibility testing. However, there is disagreement about whether the increased activity of vancomycin against gram-positive bacteria justifies its expense and toxicity for the initial empirical treatment of all patients with fever and neutropenia, especially considering that the great majority of febrile neutropenic patients will not develop gram-positive bacterial infections. Thus, on the one hand it is argued that those few neutropenic patients with documented gram-positive bacterial infections can usually be rescued by the addition of vancomycin (*41,42,44,45*), and on the other hand it is asserted that inclusion of vancomycin in the initial empirical therapy for febrile, neutropenic patients can prevent potentially fatal gram-positive breakthrough bacteremias (*6,17,40,46,47*). In a recent study of neutropenic children, vancomycin therapy was associated with little discernible toxicity (*40*), in marked contrast to previous experience with children when a less pure preparation of vancomycin was used (*48*). Thus, it appears that the decision to include vancomycin in initial empirical regimens should be based primarily on the risk of gram-positive infection in the individual patient or patient cohort, considering the particular institutional setting and antineoplastic regimen, the presence of indwelling intravascular catheters, and all other factors known to influence the incidence of gram-positive bacterial infection.

Table 2. Cost comparison of combination therapy and monotherapy (St. Jude Children's Research Hospital)

Treatment	Drug(s)	Cost per m^2 of surface area for 10-day course	
		Each	Total
Combination therapy	Vancomycin	$256.80	$917.56
	Ticarcillin	$207.00	
	Amikacin	$453.76	
Monotherapy	Ceftazidime	$492.75	$492.75

NEED FOR FURTHER RESEARCH

There is a paucity of research on the role of mucositis in the clinical course of the cancer patient. Continued support of basic studies of the pathogenesis of mucositis is fundamental to progress in this field. Clinical studies on mucositis would be

Table 3. Clinical trials comparing empirical antibacterial regimens with and without vancomycin

Reference No.	Vancomycin regimen	Non-vancomycin regimen	No. of courses (vancomycin/ no vancomycin)	Study design	Outcome
(*40*)	Vancomycin, ticarcillin, amikacin	Placebo, ticarcillin-clavulanate, amikacin	53/48	Randomized, blinded	Fewer gram-positive breakthrough bacteremias with vancomycin
(*13*)	Vancomycin, ceftazidime	Ceftazidime; cephalothin, carbenicillin, gentamicin	46/55; 105	Randomized (partially historically controlled)	No difference
(*41*)	Vancomycin, ceftazidime	Ceftazidime	44/41	Randomized	More rapid re-response of gram-negative infections to vancomycin; no difference in mortality
(*42*)	Vancomycin, amikacin, ceftazidime	Amikacin, ceftazidime	66/67	Randomized	Better response of gram-positive infections to vancomycin, but trend toward increased nephrotoxicity with vancomycin
(*17*)	Vancomycin, ceftazidime	Ceftazidime; cephalothin, gentamicin, carbenicillin	37/21; 37	Randomized (partially historically controlled	Fewer deaths with vancomycin
(*43*)	Vancomycin, aztreonam; vancomycin, amikacin, aztreonam	Moxalactam, ticarcillin	68;80/61	Randomized	Better response of gram-positive infections to vancomycin regimens
(*6*)	Vancomycin, gentamicin, ticarcillin	Placebo, gentamicin, ticarcillin	31/29	Randomized, blinded	Better response to vancomycin regimen

greatly facilitated by the development of a standard system by which mucositis (or, more specifically, breaks in the mucosal barrier) could be readily quantitated and graded. Studies to define the relationship of mucositis to the occurrence of specific systemic infections in the neutropenic cancer patient are lacking. There is still a need for well-designed, carefully conducted randomized trials addressing important questions about the choice of specific empirical antibacterial regimens for the febrile patient with mucositis and neutropenia. As is clear from a recent critical review (*49*), the vast majority of studies in this area have significant shortcomings that must be addressed in the initial design of clinical trials. From this expanding base of fundamental knowledge about the pathogenesis of mucositis, the challenge for the next decade in this field is to develop and evaluate new prophylactic and therapeutic modalities directed at mucositis and its complications.

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Nursing Management of Acute Oral Complications of Cancer

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This review evaluates the state of the science and art of nursing management of acute oral complications of cancer. Published general oral hygiene protocols are reviewed briefly, and modifications to routine nursing care for hemorrhage, infection, pain, and problems associated with radiation to the head and neck are explored. There is a scarcity of research on which to base recommendations. The literature is primarily anecdotal or based on reports of experience at a single institution. Inconsistencies among such reports are numerous and have a detrimental effect on nursing management, as various clinicians provide different patient care instruction. Known principles, e.g., the need for adequate plaque removal and infection control, form the basis for nursing guidelines. Research is needed to guide clinical decision making, especially in defining the use of toothbrush substitutes. Problems in pain management appear to arise from inadequate application of known pain management principles. Since many of the oral complications are interrelated, nursing management must also take an integrated approach, and nursing care research must be conducted in the context of multidisciplinary care. Careful transfer of current research-based knowledge to practice and future research will help to achieve high-quality nursing management of acute oral complications. [NCI Monogr 9:123–128, 1990]

This review will evaluate the current state of the science and art of nursing management of acute oral complications of cancer. In this critique, nursing care is defined broadly. Nurses and the care they provide are seen as an integral part of a multidisciplinary team effort managing all aspects of patient care. This review focuses on those facets of patient care in which nurses take a lead role in decision making, providing care, or instructing patients and families. There is a paucity of research conducted by nurse-investigators or focusing on nursing interventions. The few studies that have been done emphasize either oral assessment or mucositis management. Thus, the information that follows is drawn from investigations and practices reported by other specialists, usually dentists and dental hygienists, as well as nurses. Furthermore, this presentation will not repeat topics that are described in depth by others, such as mucositis or the selection and use of antifungal agents. After a brief review of published oral hygiene protocols, modifications to routine care for each of the following common problems are explored: hemorrhage, infection, pain, and problems associated with radiation to the head and neck.

Two goals underlie the management of acute oral complications: to reduce or relieve current conditions, and to prevent or deter development of additional complications. To achieve these goals, nursing care must employ standard oral hygiene measures as well as specific interventions targeted at the complication.

GENERAL ORAL HYGIENE PROCEDURES

Published recommendations for oral hygiene have four basic elements: assessment, brushing, rinsing, and flossing. Teaching or reinforcing oral hygiene practices is important throughout therapy.

Nurses have a key role in obtaining both baseline and ongoing assessments. These observations allow early detection of complications and monitor the effectiveness of oral care procedures. As other aspects of disease or therapy (such as nausea or fatigue) affect patients, they may no longer be willing or able to perform thorough oral hygiene. These intervening variables may deter effective oral care at the patient's most vulnerable time. Ongoing oral assessments allow nurses to recognize such changes and mobilize assistance or modifications in oral hygiene procedures.

Brushing with a soft, flexible-bristle toothbrush is recommended in order to reach all the contours of the teeth and gingival crevices. Brushing recommendations emphasize use of the Bass technique. Because mechanical action is the key to plaque removal, a choice of dentifrice is permitted. However, fluoridated toothpastes are preferred (*1*). A paste of baking soda and water may also be used (*2*). Frequency recommendations vary from a minimum of twice daily (*3*) to four times a day (*4*) to after meals and every 4 hours while awake (*5*).

Rinsing after brushing is intended to enhance removal of the loosened debris. Several rinse solutions have been suggested: hydrogen peroxide and saline, or hydrogen peroxide and water (mixed either 1:2 or 1:4) (*5*); sodium bicarbonate [1 teaspoon per cup of water (*6*) or 1 teaspoon in 500 mL of water (*5*)]; and salt (½ teaspoon), baking soda (1 teaspoon), and 1,000 mL of water (*5*).

Mouthwashes with alcohol may irritate or dry the mucosa and thus are not recommended. In addition, Wright et al. (*6*) recommend that patients form a thick paste of sodium bicarbonate and water and "pat and push" the mixture around the gingival sulcus as a complement to other dental techniques in order to decrease sulcus and pocket organisms.

Flossing with an unwaxed dental floss is the last component of published routine oral hygiene regimens. Daily flossing should be included in standard oral care (*3,4*).

Sonis and Kunz (*7*) conducted a retrospective chart review of 495 patients with cancer of sites other than the head and neck. The patients were hospitalized between 1978 and 1986, and their experience with oral complications was compared with those of a historical sample of 93 patients (*8*). During the recent evaluation period, an aggressive oral management program was instituted that included early intervention, prevention and man-

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Table 1. Published guidelines for nursing management of oral hemorrhage

Authors (ref No.)	Recommendations
Ostchega (*3*)	Stop flossing when platelet count falls to 10,000-15,000/mm^3 Stop brushing when platelet count falls to 5,000-10,000/mm^3
Daeffler (*15*)	Brushing may be contraindicated during severe thrombocytopenia Use alternative devices and methods
Daeffler (*17*)	Notify physician of active bleeding Administer therapy
Brager and Yasko (*20*)	Avoid using dental floss If platelet count is $<$ 50,000/mm^3, use sponge-tipped applicator, gauze moistened with saline, or irrigating syringe
Wright et al. (*6*)	If intraoral bleeding occurs, stop use of toothbrush, floss, and baking soda Use alternatives for cleaning
McClure et al. (*2*)	Stop brushing if it causes significant bleeding

agement by a dental team, and implementation of systematic oral hygiene measures by nurses. This combined approach resulted in 12.7% overall frequency of oral complications, compared to 38.7% in the historical sample. Although the retrospective data collection and historical comparison limit the study's findings, it is important to note that standard systematic nursing care was one of the features of the successful program.

SPECIFIC PROBLEM MANAGEMENT

Hemorrhage

Published recommendations for the oral care of patients whose platelet counts are suppressed vary greatly (table 1). Some authors indicate absolute platelet levels at which brushing must be avoided, while others emphasize "significant oral bleeding" as the criterion. Of particular concern are the frequent recommendations for substitute techniques for standard brushing and flossing routines. The inconsistencies among these recommendations make nursing-practice decisions difficult. Moreover, patients receive contradictory instructions. In critiquing these recommendations, the paucity of research made it necessary to rely primarily on established oral management principles.

The first fact to consider is well summarized by Williams et al. (*9*): "It is important to remember that bleeding can be a sign of gingival inflammation produced by the accumulation of plaque, even in the thrombocytopenic patient." Plaque must be removed effectively; allowing plaque to remain contributes to the bleeding problem. Plaque removal requires the mechanical action that has been shown to occur in toothbrushing. However, many recommendations suggest using alternatives, such as toothettes or gauze-covered tongue blades. How effective are such alternatives in plaque removal?

Two small studies, one of which is unpublished, examined the effectiveness of the device known as a toothette, a short stick with a sponge attached that is often impregnated with mint flavoring. In 1975, DeWalt (*10*) studied the effectiveness of a toothbrush versus a toothette in removing oral debris when used at various regular intervals, i.e., every 2, 3, or 4 hours, among 48 geriatric patients. The variables examined were salivation, tongue moisture, tongue color, moisture of palates, color of gingiva, condition of membranes, lip texture, lip moisture, and soft tooth debris. Twenty of the 48 subjects were edentulous, and the 48 subjects were divided into six groups, which greatly limits interpretation of the study. However, the toothbrush, used at 2-hour intervals, gave better scores for both removal of soft tissue debris and gingival tissue ($P = .05$). Scores for salivation, tongue moisture, moisture of the palates, and lip moisture were improved by toothette usage, but it was not a statistically significant improvement. The author concluded that the deteriorating scores for 10 subjects (whether they were edentulous is unknown) was associated with the abrasive qualities of the toothbrush. This statement is similar to the frequently offered rationale for stopping toothbrushing, namely, to avoid traumatizing the mouth.

The other known study comparing toothettes and toothbrushing was conducted by Heery (*11*) in 1984. Sixty adults were assigned randomly to toothette or toothbrush use for 3 minutes, employing the Bass technique. Measurement of disclosed plaque was determined by using the Patient Hygiene Performance Index of Podshadley and Haley (*12*). Six teeth were assessed: maxillary right first molar, maxillary right central incisor, maxillary left first molar, mandibular left first molar, mandibular left central incisor, and mandibular right first molar. A two-tailed *t*-test was used to compare plaque removal. The toothette group had significantly more plaque remaining than the toothbrush group ($P = .001$). The study is limited by having only one rater and the need to devise a procedure for use of the toothette (i.e., use like a toothbrush with the Bass technique).

Clearly, these studies warrant replication, especially among cancer patients, whose oral conditions differ from those of the subjects in both studies. The concern remains that the toothette does not provide adequate plaque removal, which may contribute to the bleeding problem. If toothettes and other techniques are to continue as substitutes for toothbrushing, further research is warranted to determine whether they are beneficial. The effectiveness of the alternatives and when or how they could be combined with toothbrushing are the issues.

It appears that some recommendations for oral care in the presence of low platelet counts are not based upon ongoing oral assessment. The authors listed in table 1 state that there are absolute levels of thrombocytopenia that necessitate stopping toothbrush use. Instead, the response of the mouth to brushing should be monitored, as patients can tolerate brushing without evidence of bleeding at widely different platelet levels. Factors such as the condition of the gingiva influence bleeding, and the platelet level need not be the sole determinant. Such absolute guidelines can cause substantial patient confusion. For example, patients brush their teeth at home without bleeding difficulties, and 2 hours later in the clinic are told that this is "dangerous."

Intraoral bleeding warrants prompt intervention. Topical thrombin should be available on patient care units with standing orders for its use. In situations when intraoral bleeding occurs

often, dental mouth guards can be made early in the patient's treatment. These devices, prepared by dental specialists, allow nurses to apply thrombin in the device, making management easier. Platelet transfusions may also be warranted. Guidelines for platelet administration are beyond the scope of this discussion.

In summary, nursing care of the cancer patient who may experience oral hemorrhage requires continual monitoring of the patient's response to lowered platelet counts. Interventions to ensure effective plaque removal must be continued whenever feasible. Topical thrombin treatment with or without platelet administration may be required.

Ulceration

Ulcerations and infections are linked together because of the potential for ulcerations to become infection sites. In both the 1978 and 1988 reports on the incidence of oral problems by Sonis and colleagues (*7,8*), ulceration is the most common oral problem. Ulcerations can be induced by cancer chemotherapy as part of the damage described under mucositis or by local irritation and trauma. Chemotherapy-induced ulcerations that remain uninfected can heal as the mucosa regenerates. Baseline evaluation of the mouth should identify any rough tooth surfaces from broken teeth, faulty restorations, or faulty appliances that could cause local trauma. Such problems are best corrected prior to therapy. The nurse must be vigilant to changes in the mouth indicative of new sources of local trauma. For example, when changes occur in the oral tissue, dentures may no longer fit well and cause local irritation. Samples from suspicious areas should be cultured. Nursing management demands that the oral cavity be kept as clean as possible to prevent colonization, especially by normal flora, and that prophylactic antifungal and antibacterial regimens be carried out conscientiously.

Infection

The recent chart review by Sonis and Kunz (*7*) shows that 27% of the oral complications documented (29 problems) are bacterial, viral, or fungal infections. When the incidence of gingivitis is added (16 problems), 42% of the complications are infections. Viewed this way, infections are a greater problem than ulceration and mucositis combined (42% vs. 28%). The danger of oral infections becoming the source of septicemia has been underscored repeatedly. Nursing care is described in three parts: patients at risk, control of infection, and application of therapeutic methods.

Patients at Risk

Periodontal disease is a chronic, inflammatory disease, including both gingivitis and periodontitis, that occurs in most Americans. Thus, nurses need to consider most cancer patients as having an increased risk of oral infection. The primary cause is plaque, whose bacterial toxins can cause gingival bleeding in healthy individuals (*9*). Nurses must also be aware that most patients have an infectious process ongoing in their mouths that requires effective plaque removal, even though symptoms of infection may not be present. In a study of 22 acute nonlymphocytic leukemia patients by Overholser and colleagues (*13*), 23% (14 of 47) of oral infections originated in the periodontium. Underlying periodontal disease should be considered a potential cause of oral infections as well as a cause when fever of unknown origin develops. Overholser and colleagues (*13*) used a protocol of dental debridement consisting of brushing and flossing along with warm saline and 3% H_2O_2 rinses to control the infection.

Dental manipulation is another potential infection risk. Thorough oral evaluation and dental intervention prior to the initiation of cancer therapy often are not possible in the context of an urgent need to treat tumors. Toth and Frame (*14*) state the problem clearly: "any form of dental manipulation, including extraction, root canal therapy, dental prophylaxis or simple probing, produces a significant bacteremia." In this situation, nursing management emphasizes minimizing the consequences of the bacteremia by (*a*) scheduling dental procedures when blood cell counts are at or near their peak and expected to remain there for 5–7 days (*14*) and (*b*) ensuring that both nurses and patients understand what procedures were performed and any special oral care instructions. If more extensive dental procedures are required, such as removal of an abscessed tooth, nursing care must include meticulous post-oral surgery efforts to keep the mouth clean and avoid perpetuating the infection.

Control of Infection

Much of nursing literature addresses the management of oral infections, with the primary focus on selection and use of pharmacologic agents. Modifications of oral hygiene procedures are also considered, often indicating that routine brushing and flossing should be stopped in the neutropenic patient. However, more recent literature indicates that brushing and flossing should be done. As in situations with hemorrhage, recommendations to limit brushing and flossing may cause patients harm, as they allow plaque with its bacteria to proliferate unchecked. Oral care in the presence of infection can be difficult because of the tenacity with which exudates adhere to oral structures, the compounding of debris, plaque, medication, and exudates, and oral pain, which is discussed separately.

In reviewing the literature on nursing management of oral infection, the scarcity of information about avoiding the spread of infection causes particular concern. Dentures and other removable appliances, their containers, and cleansing solutions have been identified as potential reservoirs of pathogens, and procedures to clean appliances in uncontaminated solutions and store them carefully in clean containers have been outlined. It is reasonable to use standard techniques to avoid the spread of infection, such as isolating and disposing of garbage and sterilizing instruments. However, published reports of nursing procedures exclude these and other basic precautions. It can be hypothesized that such directions are included in hospital infection control guidelines, but the lack of reference to infection control precautions raises concern about their actual use. Oral hygiene and topical medication procedures to ensure containment of the infection are not specified. Protective gloves are a reasonable precaution to avoid spreading organisms to other parts of the patient's body or to the caregiver. Lesions, such as herpes, may occur on the lips and should be handled with the same precautions as other oral lesions, rather than be managed as part of cleansing the face. An integral part of nursing management of oral infections is teaching patients and families not to touch the mouth and then other parts of their bodies. The principles of infection transmission should be included in nursing management guidelines for oral infections

among cancer patients. The basics of good patient management appear to require brushing and flossing coupled with diligent application of the principles of infection control.

Irrigation is a frequently suggested modification of oral hygiene procedures, particularly in the presence of oral infection. Irrigation can assist in removing loose debris, and many instruments have been suggested, such as a Power Spray, a Water Pik, an enema bag with a No. 14 French catheter, and a bulb syringe (*15*). No research reports that examined irrigation methods were found. The main advantage of irrigation appears to be its soothing nature, which is beneficial if patients then become more willing to use the technique. However, several issues warrant consideration. Some clinicians express concern that irrigation devices may force bacteria into ulcerations and other gingival pockets, thereby harming the patient. Is mechanical action adequate to remove microorganisms? Are certain irrigation pressure levels dangerous? What is the proper technique in terms of angle of flow against the gingiva? Can irrigation be used safely in the context of an overall oral hygiene protocol? If so, should it be done before or after brushing and flossing?

Use of Therapeutics

Others have presented information about selection and use of therapeutic methods to control infection. The primary nursing role is administration of drugs and patient teaching. Basic principles apply, namely, cleansing the area first with techniques to control spread and using an applicator or gloved finger to apply the agent. Local effects are achieved by having the agent remain in contact with the infected area. Patients should receive instructions not to eat or drink, typically for 30 minutes after application.

Oral Pain

Hemorrhage and infection often occur together, particularly among patients experiencing bone marrow suppression. In many situations, care may be governed by the dominance of oral pain. In fact, intense oral pain may be the true force guiding clinicians in the management of oral complications. Thus, conclusions about the state of the art of nursing management of oral complications must examine oral pain.

The principles of oral pain management are the same as for other cancer-related pain: careful assessment of the history of the pain along with examination of the patient; direct treatment aimed at the cause of the pain combined with pain relief; and monitoring the effectiveness of interventions (*16*).

Several sources of oral pain can be identified by the nurse. The key role for nursing is correct identification of the source of the problem. Chills and fever may cause patients to clamp their teeth closed for prolonged periods. Observation of patients is important to recognize this clamping behavior and prosthodontic assistance should be provided. A tooth guard can be made to absorb the stress, reducing the tooth and jaw pain it causes (*14*). Another source of pain is tooth decay or abscess formation due to inadequate oral hygiene. It is not the nurse's role to differentiate tooth decay from abscess. Rather, nurses should ensure that patients use fluoride to prevent caries and inform dental specialists about the site and characteristics of the pain.

Local agents may be effective in controlling oral pain, especially mild pain associated with only a few ulcerations (table 2). Several nursing implications are important to note in using topical agents. The duration of action varies, but is generally short (20 min to 1 hr). Local agents are often adequate to provide relief for meals, and thus the use of topical agents prior to eating is frequently recommended. A significant limitation of topical agents is the brief duration of their effects, i.e., they only provide spot relief three to four times per day, which may not be adequate.

Table 2. Topical anesthetics for oral pain management

Xylocaine (lidocaine) viscous solution 2%
Dyclonine hydrochloride 0.5%
Diphenhydramine hydrochloride liquid
Benzonatate NF (100 mL/Perle)
Cetacaine (benzocaine) 20% solution
Orabase (hydrocortisone acetate) with benzocaine

To be effective, topical agents must reach the affected area, which means that debris must be removed first. While this is logical, it may be difficult to do. Patients may have too much pain to allow thorough oral hygiene. If patients are refusing oral care before use of a topical agent, nurses must question whether the topical agent alone can achieve relief. Systemic medication is probably indicated, with topical agents supplementing the drugs at times of potential pain increase, e.g., when cleaning the mouth or eating. Once the pain has been stabilized through medication, performing oral care before application of the topical agent may not be an issue.

Topical anesthetic agents can be sprayed on, applied directly to painful areas, or swished and swallowed or expectorated. When such agents are used in the presence of infection, nurses and patients must take care not to spread the infection. Wearing gloves when touching the mouth is important for caregivers.

It is important to monitor the side effects of topical agents. Dyclonine hydrochloride (Dyclone) 0.5% decreases the gag reflex. Temperature sensitivity may be reduced with local anesthetics. As topical anesthetics are frequently administered before meals, excessively hot (in temperature) foods should be avoided and care should be taken to see that the patient is swallowing safely. The directions sometimes call for the patients to swallow, rather than expectorate, the medication. When treating with viscous lidocaine, observe for systemic effects, such as central nervous system depression or excitation (*17*). Increased frequency of self-administration may be the patient's way to cope with inadequate oral pain management and may result in overdosing and unplanned systemic effects. Ongoing pain assessment to determine the adequacy of relief may prevent such complications. The incidence and duration of extensive oral pain are poorly documented in the literature. When local therapy is inadequate, systemic analgesic agents are indicated.

According to the principles of pain management, nonnarcotic, narcotic, and adjuvant analgesic drugs should be used in increasing levels of potency to achieve relief. The route of administration should be selected carefully because swallowing pills may be difficult and may increase the pain. Medications should be given at regularly scheduled intervals to achieve a steady-state level (*16*). As acute problems resolve, reductions in pain medication can be anticipated.

Acute Complications of Radiation Therapy

External-beam radiation therapy to the head and neck region causes several acute problems. Patients are "most likely to experience side effects when high doses (> 4,500 cGy) are administered in larger fields including both sides of the mouth, jaws and associated salivary glands" (*18*). This discussion will focus on xerostomia, radiation caries, and radiation implants.

Xerostomia

Radiation effects on the salivary glands have major consequences. Lack of saliva is more than a mere inconvenience to patients. Whether or not the changes in the salivary glands are permanent depends upon the total dose of radiation received, with approximately 6,000 rads being the dividing point between acute, reversible problems and a chronic situation (*19*). Patients experience dry mouth at the beginning of treatment, with progression to thick and viscous saliva within 2 to 3 weeks, followed by significant reductions in saliva volume. Numerous problems can be attributed to decreased saliva: increased cariogenic bacteria levels, resulting in rapidly forming dental caries and increased severity of caries; increased incidence of periodontal disease; less tolerance to prosthetic devices; decreased taste acuity; and difficulties with mastication and swallowing. The goals of management are stated by Sonis (*19*) and summarized here as (*a*) stimulation of existing salivary flow, (*b*) replacement of lost secretions, (*c*) protection of the dentition, and (*d*) reduction of sucrose intake.

Patients are encouraged to suck on sugar-free candies to stimulate salivary flow. The potential contribution of many such candies to tooth decay is unknown. Saliva substitutes, designed to replace lost secretions, have the physical characteristics of saliva but do not actually reproduce the functions of normal saliva, e.g., they lack antibacterial factors (*6*). Water also provides symptomatic relief. Dietary recommendations are appropriate, e.g., eating foods with a high moisture content and drinking lots of liquids with meals to ease mastication. Efforts to replace lost secretions will frequently increase patient comfort, but they will not replace the vital functions of the saliva in terms of maintaining oral pH, electrolyte, and immunoglobulin levels.

Radiation Caries

Protection of dentition is a goal related to xerostomia management as well as a major problem of head and neck radiation, namely radiation caries, and is vitally important given the significant contributions that saliva normally makes. The need for daily application of fluoride has been well documented. Dental specialists will develop an appropriate applicator tray. The primary nursing responsibility is to ensure compliance, largely by instructing patients and families about the importance of the fluoride and proper application techniques. As fatigue increases throughout therapy, it may become necessary for others to provide the oral care and apply fluoride.

Radiation Implants

Radiation sources placed directly into oral cavity structures, typically the tongue, produce acute problems. The acute oral problem requiring the greatest vigilance is swelling around the implant. Such swelling poses the danger of airway obstruction, and therefore nursing actions must include frequent assessment. Often a nasogastric tube is inserted prior to therapy, which further compromises the potential air passage space. The patient's position is important, and a semi-Fowler's position is usually adopted. Mucositis and infection are other problems that can be anticipated. Oral hygiene measures can be difficult to execute and often are limited to oral rinsing or irrigation due to realistic fears of dislodging the radiation source. Nurses need to assess whether some portions of the mouth, e.g., the contralateral side to the radiation implant, can be brushed with a small (child's) toothbrush. There can be no universal directions because of the special circumstances surrounding each patient's therapy. However, recognition of the potential complications associated with inadequate plaque removal should guide nurses to assess each individual case carefully.

CONCLUSION AND FUTURE DIRECTIONS

Through review of the problems of hemorrhage, infection, pain, and radiation therapy and attendant nursing care, it is evident that there is a scarcity of research on which to base recommendations. The published literature is primarily anecdotal or based on reports of experience at a single institution. Inconsistencies among such reports are numerous and have a detrimental effect on nursing management, as various clinicians provide different patient care instructions.

Recommendations for care are primarily derived from known principles, e.g., the need for adequate plaque removal and infection control. The following methods of oral management should be evaluated in scientifically rigorous trials:

(*a*) Efficacy of alternatives to toothbrushing: A trial comparing toothettes, gauze wrapped around a tongue blade, or a small toothbrush could be done.
(*b*) Use of complementary techniques, e.g., oral irrigations: When and how should irrigations be employed? A trial could compare the effectiveness of swishing and expectorating with various irrigation techniques. Is the timing of irrigation (before or after brushing) more effective, more comfortable?

These techniques need to be studied in the context of the oral problems described at this conference. However, documentation of effect in normal subjects may provide clearer direction for the appropriateness of pursuing these issues.

Pain assessment and management are an integral part of nursing management. Topical anesthetic agents are limited greatly by their short duration of action. Nurses must assess whether systemic agents are required to relieve the pain and then follow known management principles. Pain management has been well studied and guidelines have been developed. The issue requiring attention is the use of these techniques to manage oral pain.

I have not examined current research on patient self-care because the focus is not on oral care trials. However, the efficacy of different approaches to having cancer patients manage numerous symptoms associated with both chemotherapy and radiation therapy is the subject of several currently funded projects. These researchers are also examining the characteristics of people who do and do not perform self-care. This information will be useful in developing future nursing management techniques of oral care because the majority of

patients are treated on an outpatient basis, which necessitates self-care.

Since many oral complications do not occur in isolation but are interrelated, nursing management must similarly take an integrated approach, and nursing care research must be conducted in the context of multidisciplinary care. Careful transfer of current research-based knowledge to practice, and future research will clear the path to achieving high-quality nursing management of acute oral complications of cancer.

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Oral Complications in the Pediatric Population

Penelope J. Leggott[1,*]

Cancer is the second most common cause of death in children, and an increasing number of children are diagnosed annually with malignant disease. Approximately 6,600 children in the United States will be diagnosed with cancer this year, and about 1,800 children will die from malignant disease, primarily leukemia. Acute lymphoblastic leukemia (ALL) constitutes 80% of all leukemias in children. In the last 40 years there have been dramatic advances in the treatment of children with malignant disease. In the late 1940s, children with ALL, for example, could expect a median survival of only 3 months, but now 95% achieve complete remission, with more than 55% in continuous remission at 5 years (*1*). Other malignant conditions, such as Wilms' tumor, also have a much improved prognosis in recent years (*2*). Current treatment protocols for malignant disease may include combination chemotherapy, given either alone or with additional chemotherapy or radiation therapy. While the lower mortality rates are encouraging, the morbidity associated with the treatment regimens remains high (*3*).

Oral complications during therapy are a frequent cause of morbidity in both adult and pediatric cancer patients. The cytotoxic effects of anticancer agents and radiotherapy cause disruption and breakdown of the oral mucosal barrier, allowing the development of infection by resident oral microflora. The oral complications include mucositis and ulceration, candidiasis and other oral infections, oral hemorrhage, pain, gingival inflammation, and xerostomia (*3,4*). Oral infection may pose significant risk of systemic spread and compromise the child's clinical course. Moreover, severe pain associated with oral lesions may contribute to compromised nutritional intake.

The majority of publications on oral complications associated with cancer therapies focus on adult patients. Wahlin and Matsson (*5*) include children in their study, and a number of reviews specifically address the problems of the pediatric patient (*6–8*). However, only a few studies present data on oral complications in children (*9–12*), although more recently attention has been directed to oral complications and their management in pediatric bone marrow transplant patients (*13–15*). Two studies (*10,12*) reported that the frequency of oral complications in pediatric cancer patients was three times higher than in adults. The authors suggest that the increased mitotic index in young patients makes them more susceptible to the effects of chemotherapy.

It has been suggested that patients receiving chemotherapy for hematological malignancies tend to develop oral complications at a higher rate than do patients with other forms of cancer. Barrett (*16*) found oral complications in 89% of adult patients with acute leukemia. Sonis et al. (*17*) reported that more than two-thirds of the patients with leukemia developed some form of oral complication during treatment, whereas only one-third of the patients with non-Hodgkin's lymphoma (NHL) developed oral complications. However, with the addition of anthracyclines to the treatment regimens for NHL, oral complications are being seen more frequently (*18*).

In general, the nature and degree of the oral complications appear to depend on a number of factors: type of malignancy, age of the patient, location and dosage of radiotherapy, fractionated versus whole-dose radiation, total dosage and timing of chemotherapeutic agents, prophylactic regimens for *Candida* species, herpes simplex virus, and other potential pathogens, prior oral status, and level of oral care during therapy (*3,4,10,19–22*). In addition, the presence and extent of mucosal lesions vary during different phases of treatment, reflecting cytotoxicity and the degree of myelosuppression (*5*).

ORAL MUCOSAL CHANGES

The most common oral complications associated with cancer therapy are ulceration and mucositis (*3,4*). Onset usually occurs at the nadir of the wbc count and resolves as the absolute neutrophil count recovers. Clinically, the mucosal tissues involved are erythematous, the most affected areas being the soft palate, pharynx, buccal mucosa, and sublingual tissues. Ulcerations are most commonly found on areas most often exposed to minor trauma, including the lips, buccal mucosa, and tongue. The severity and duration of mucositis depend on a number of factors, particularly the use of therapeutic agents such as methotrexate, melphalan, and total-body irradiation (*23*). There are few data comparing mucosal changes in children and adults.

The management of mucositis is generally limited to the relief of pain, and a variety of topical treatment agents are in use, including topical anesthetics, coating agents such as sucralfate, sodium bicarbonate rinses, and chlorhexidine mouthrinses. There are no definitive studies to indicate that one treatment is more effective than another, although the use of chlorhexidine mouthrinse in adult bone marrow transplant patients shows promise (*24*). Ulcers suspected of being secondarily infected should be cultured and tested for antibiotic sensitivity (*7*). In severe cases, a morphine drip may be necessary for pain management. A number of authors have suggested that patients who used a supervised mouth care protocol experienced less severe mucositis than those who did not (*20,25–29*), but not all authors agree (*30*).

INFECTIONS

The patient is at greatest risk for oral infection during the period of immunosuppression and neutropenia, and particularly when there is loss of mucosal integrity. The oral tissues are at

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risk for infection by a number of indigenous organisms, including bacteria, viruses, and fungi.

Oral Candidiasis

Oral candidiasis is a common fungal infection in cancer patients and may be associated with the vigorous use of antibiotics or steroids. Scully and MacFarlane (*11*) reported a higher incidence of oral candidiasis in children with leukemia than in those with lymphoma. A serious complication of oral candidiasis is the development of systemic candidiasis. In some centers nystatin is used as a prophylactic agent. However, more effective preventive protocols are now available, including multiagent regimens and 0.12% chlorhexidine mouthrinse (*15,24,25*). Treatment regimens for oral candidiasis, in addition to nystatin, are clotrimazole, ketoconazole, and amphotericin B.

Oral Bacterial Infections

Oral bacterial infections by species of *Pseudomonas*, *Klebsiella*, and *Staphylococcus* have been described in adults (*4*). In contrast, Scully and MacFarlane (*11*) failed to demonstrate noncommensal organisms in 44 children undergoing cancer treatment. The majority of oral infections result from secondarily infected oral ulcerations (*7*) and are treated with appropriate antibiotics. Dental caries and pulpal infection may compromise a child's cancer treatment, and there is general agreement that all children should have any necessary dental restorations or extractions completed at least 10 days prior to commencing cancer therapy. Gingivitis, and periodontal disease in an older child, may also adversely affect the child's status, and good preventive care is an important adjunct to management. In immunosuppressed individuals, clinical expression of the inflammatory process may be markedly reduced and complicate diagnosis (*31*).

Viral Infections

Herpes simplex virus (HSV) infection is not a frequently reported complication in children. However, Scully and MacFarlane (*11*) reported that 27% of their pediatric patients developed HSV infection during chemotherapy, most of whom had no previous history of HSV infection. It is frequently difficult to differentiate mucositis from viral infection, and as mentioned previously, ulcerated oral lesions should be cultured to determine the diagnosis. Routine culture of the oral mucous membranes of children with mucositis demonstrates a higher incidence of HSV than was previously suspected (Zoger S: personal communication). Acyclovir is the therapeutic agent of choice. In some centers, acyclovir prophylaxis has been used with success, particularly with children undergoing bone marrow transplantation (*32*). Herpes zoster infection, while a theoretical infectious problem, has not been identified as a significant problem in children.

XEROSTOMIA

Both chemotherapy and radiotherapy may result in toxicity to the salivary glands, producing pain, swelling, xerostomia, and fever. The patient may have difficulty swallowing, eating, and speaking. In adults and older children treated with fractionated total-body irradiation, this condition usually resolves spontaneously within 48 hours. In contrast, prepubertal children do not usually suffer from these complications when treated with fractionated-radiation therapy (*15,29*). Radiation therapy to the head and neck is associated with permanent consequences to the salivary tissues in all patients (*21*). Xerostomia-associated discomfort is relieved by synthetic saliva substitutes, such as Salivart and Xerolube, the use of a spritz bottle with sterile water, lip balm, and sugar-free pastilles (*33*).

HEMORRHAGE

The prevalence of this complication in children is not clear. Spontaneous bleeding may occur during the period of immunosuppression and neutropenia, particularly if platelet counts drop below 15,000 cells/mm^3 (*15*). However, platelet infusion is usually instituted when thrombocytopenia threatens the patient's management. Oral bleeding occurs most often from the gingival tissues, particularly in patients with poor oral hygiene (*7,9*) but may also occur from ulcerative lesions. Wahlin and Matsson (*5*) reported that oral hemorrhage was more common in adult patients with acute myeloid leukemia (AML) than children with ALL, and the most frequent locations were the buccal mucosa, palate, and floor of the mouth. An age-related susceptibility to hemorrhage remains to be investigated. Formation of petechiae or hematomas as a result of trauma may occur when platelet counts are low. Topical thrombin can be used to control minor oral bleeding. Amicar and Avitene have also been used with success (*23*).

PREVENTIVE ORAL PROTOCOLS

In general, preventive protocols have been developed for adults and are based on subjective observations as a result of experience rather than long-term clinical studies (*20,34–39*). The use of chlorhexidine has been extensively documented in Europe and appears to hold promise for pediatric patients (*25*) but has only recently been studied in the United States (*24*) in adult bone marrow transplant patients. No specific, integrated protocols have been developed for children. However, from the limited data, it is clear that all sources of oral infection, such as dental caries, abscessed teeth, and gingivitis, should be resolved prior to cancer therapy. During therapy, an oral care program for children is needed that includes oral hygiene methods appropriate for the child's medical status, an antimicrobial agent for the prevention of secondary infection, and a caries prevention regimen. In addition, supervision and, if necessary, provision of oral care for pediatric patients should be given by appropriate personnel. This mandates the education of health care professionals, including nursing personnel, in a comprehensive team approach to oral care. Long-term oral health maintenance of pediatric cancer patients is also necessary, because studies on the late effects of cancer treatment in children indicate a higher incidence of caries, tooth abnormalities, and gingival inflammation than in control subjects (*12,40,41*).

SUMMARY

A number of acute oral complications may be associated with cancer therapy in children, but the extent and duration of these complications, and the most effective management techniques,

have not been well described. The few studies differ in design, making comparisons difficult. Well-controlled, prospective clinical studies are needed to define the most effective strategies for the management of acute oral complications in children. However, it is clear that dental intervention prior to cancer therapy is an important factor in the optimal preparation of the patient. During cancer therapy, intensive supervised oral preventive protocols appear to be of benefit to the child's oral health, overall comfort, and well-being. Furthermore, the prevention of oral infection may significantly reduce the morbidity associated with cancer therapy. Long-term preventive oral care may help prevent dental disease and infection in medically compromised children and contribute to improving the quality of life.

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V. Management of Chronic Problems

Recognition, Incidence, and Management of Oral Graft-Versus-Host Disease

Mark M. Schubert,* Keith M. Sullivan

Acute and chronic graft-versus-host disease (GVHD) are significant complications of allogeneic bone marrow transplantation that occur when immunologically active T-cell lymphocytes are transplanted into an immunosuppressed recipient who is genetically disparate from the marrow donor. Oral GVHD lesions closely resemble those seen with a number of autoimmune connective tissue diseases, including lichen planus, systemic sclerosis, lupus erythematosus, and Sjögren's syndrome. Mucosal erythema, atrophy, and ulceration are noted clinically; lichen planus-like lesions are the most distinctive oral lesions. Salivary gland changes include changes in both flow rate and sialochemistry. Oral involvement ranges between 33% and 75% for patients with acute GVHD and upwards of 80% for those with chronic GVHD. Management of oral GVHD lesions depends on successful systemic therapy, although topical steroids can be of help in some instances. [NCI Monogr 9:135–143, 1990]

The first clinically successful bone marrow transplants (BMTs) were carried out in the late 1950s (*1*). A number of complications, however, presented obstacles to the more extensive use of BMT; among the significant problems were infections, hemorrhage, graft failure, recurrent malignant disease, and graft-versus-host disease (GVHD). Since the 1960s, advances made in histocompatability typing, pretransplant conditioning, posttransplant immunosuppressive prophylaxis, supportive care, and infection control have allowed BMT to evolve from an experimental form of therapy for end-stage disease to the preferred treatment for a number of hematologic disorders. However, despite the use of HLA-identical donors and the administration of posttransplant immunosuppressive drugs, GVHD remains a significant complication for patients undergoing allogeneic BMT.

GVHD occurs when genetically disparate but immunologically active lymphoid cells (T-cells) are transplanted into an immunosuppressed recipient incapable of rejecting the graft (*2–4*). The transplanted T-lymphocytes recognize histocompatibility antigens of host tissues as foreign, become sensitized, proliferate, and directly or through secondary mechanisms attack recipient tissue. When moderate to severe disease occurs, it can be associated with reduced survival due to immunologically mediated organ dysfunction and profound progressive immunodeficiency, with death usually resulting from infection (*3,5,6*). Alternatively, survival in patients with advanced malignancies may be improved due to a graft-versus-leukemia effect associated with GVHD (*7,8*). Both an acute and a chronic form of GVHD have been described (table 1). Whether the two forms of GVHD are the same disease or separate diseases with different mechanisms is still uncertain (*4*). While it is generally considered that acute GVHD is an alloimmune disease, the genesis of chronic GVHD and the relative contributions of alloimmunity and autoimmunity are less clear. Clinicians have attempted to match patient and marrow donor as closely as possible in terms of major histocompatability complex (MHC) antigens in order to reduce the risk of GVHD. However, it is clear that minor histocompatability antigens as well as other factors also contribute to the incidence of GVHD in HLA-identical siblings and contribute to a GVHD-like syndrome occasionally reported in identical twin (syngeneic) and autologous transplant recipients (*9–11*).

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD occurs in the first 100 days posttransplant, with the median day of onset being day 19 posttransplant. The incidence of acute GVHD varies considerably between transplant centers and even within the same institution depending on the presence of risk factors associated with acute GVHD or its prevention. Among the more important risk factors are the degree of histocompatibility transplantation antigen disparity between donor and recipient, age of recipient, sex and parity of donor, and exposure to herpes virus (*3,12–18*). Reports from Seattle include a range in incidence between 18% and 70% for HLA-matched recipients receiving GVHD prophylactic immunosuppression and 100% for those not receiving posttransplant immunosuppressive prophylaxis (*19–21*). Two recent studies have reported that the incidence of histologically proven acute GVHD among autologous and syngeneic transplants ranges between 11% and 33% and possibly as high as 78% (*22–23*). However, most centers rarely, if ever, observe fatal GVHD after autologous or syngeneic transplantation. The morbidity and mortality related to acute GVHD are directly related to the severity of the disease. Acute GVHD was responsible for 40% of the deaths in a series of allogeneic patients receiving transplants at The Johns Hopkins Hospital (*24*). In a study reported by Storb et al. (*25*), 88% of patients with no or only mild cutaneous acute GVHD survived, compared to only 45% with stage II (mild) to IV (severe) acute GVHD. Advances in the

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Table 1. GVHD in allogeneic marrow transplant patients with HLA-matched sibling donors[a]

GVHD type	Frequency (%)	Onset posttransplant	Target organs
Acute	35-70	Before day 100	Skin, liver, gut, mouth
Chronic	25-45	After day 100	Multiorgan "autoimmunity"

[a]Data are from references *19* and *21*.

treatment and supportive care of patients with GVHD have decreased the mortality of the disease (*19*).

The diagnosis of acute GVHD can be difficult (*26*), and the differential diagnosis includes the effects of chemoradiotherapy toxicities, antibiotic reactions, and infection-induced complications (*3*). Diagnosis and grading of acute GVHD are based on a spectrum of clinical and laboratory features (*3,27,28*) (table 2). Clinically acute GVHD is characterized by cutaneous rashes, liver involvement associated with elevated hepatic function tests, and gastrointestinal involvement manifested as abdominal pain, nausea, vomiting, anorexia, diarrhea, and intestinal bleeding (*3,5,13*). Acute GVHD is characterized histologically by dermatitis, enteritis, and hepatitis (*4*).

A number of different strategies to prevent acute GVHD have been explored (table 3). Prevention centers on selection of donors who are as histocompatible as possible with recipients. Other strategies include supportive care (infection prevention and treatment and parenteral hyperalimentation) and immunosuppressive prophylaxis (*24,29*). Prophylactic immunosuppressive therapies have included posttransplant administration of methotrexate (MTX), cyclophosphamide, antithymocyte globulin (ATG), cyclosporine (CSP), or combinations of MTX and prednisone, MTX plus ATG and prednisone, and MTX and CSP with or without prednisone (*24*). In vitro purging of T-cells from donor marrow prior to infusion has shown encouraging results in reducing acute GVHD, but has failed to show improved overall survival due to increased rates of graft rejection and recurrent leukemia (*24,29*). Other strategies have included total lymphoid irradiation, thymic transplantation, and the use of sterile environment and gut decontamination (*3*).

Treatment of established acute GVHD can be difficult. Therapy has centered around the use of ATG, prednisone, CSP, or combinations of ATG and CSP with or without prednisone. Therapy for patients with steroid-resistant acute GVHD with anti-T-cell treatments has not improved survival significantly (*3,30,31*). Recent anecdotal reports of the use of thalidomide for acute GVHD require confirmation and further study (*32–35*).

CHRONIC GRAFT-VERSUS-HOST DISEASE

The onset of chronic GVHD occurs between 100 and 400 days post-BMT (*5*). It can progress directly from acute GVHD, occur following previous resolution of acute GVHD, or, in 20%–30% of the cases, can have a de novo late onset without evidence of prior acute GVHD. Similar to acute GVHD, the incidence of chronic GVHD will vary with the immunologic risk factors. Chronic GVHD develops in between 25% and 40% of long-term survivors of allogeneic BMT (*6,36*). Factors that have been shown to predispose to chronic GVHD include prior acute GVHD, increasing patient age, and use of viable (nonirradiated) buffy coat cell infusions (*6,25,37,38*). There is controversy over the role of risk factors of chronic GVHD, such as increasing donor age, prior cytomegalovirus (CMV) infection, immune status, and use of total lymphoid irradiation (*1,39,40*). Because it involves many organs, chronic GVHD can cause significant morbidity and disability, with more than 80% of untreated patients maintaining a Karnofsky performance score of less than 70% (*15*).

Chronic GVHD may result from an interplay of alloimmunity and immune dysregulation, leading to severe immunodeficiency (*3,4*). Immune factors that have been implicated in influencing chronic GVHD include thymic dysfunction, alloantigen-nonspecific suppressor cells, and inability to generate antigen-specific suppressor T-cells (*4,40,41*). In addition to the direct damage to host tissues caused by these reactions, there can be significant immunodeficiency that places patients at high risk for infections, especially with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (*42*).

Clinically, pathologically, and in laboratory results, chronic

Table 2. Clinical staging and grading of acute GVHD[a]

Stage or grade	Skin	Liver	Gut	Functional impairment	% Surviving
Stage					
1+	Maculopapular rash <25% body surface	Bilirubin 2-3 mg/dL	Diarrhea 0.5-1.0 L/day		
2+	Maculopapular rash 25%-50% body surface	Bilirubin 3-6 mg/dL	Diarrhea 1.0-1.5 L/day		
3+	Generalized erythroderma	Bilirubin 6-15 mg/dL	Diarrhea > 1.5 L/day; cramping, pain, nausea		
4+	Desquamation and bullae	Bilirubin > 15 mg/dL	Severe pain ± ileus		
Grade					
0 (none)	0	0	0	0	89
I (mild)	1+ to 2+	0	0	0	93
II (moderate)	1+ to 3+	+[b]	+[b]	+	58
III (severe)	2+ to 3+	2+ to 3+[b]	2+ to 3+[b]	2+	68
IV (life-threatening)	2+ to 4+	2+ to 4+	2+ to 4+	3+	0

[a]Data are from references *3, 19, 25, 103,* and *104*.
[b]Liver or gut, not necessarily both.

Table 3. Prevention of GVHD[a]

1. Histocompatibility matching of donor and recipient
2. Immunosuppression (in vivo prophylaxis)
   a. Methotrexate (MTX)
   b. Cyclophosphamide (CY)
   c. Antithymocyte globulin (ATG)
   d. Cyclosporine (CSP)
   e. MTX + prednisone
   f. MTX + ATG + prednisone
   g. MTX + CSP + prednisone
3. Protective environment and gut decontamination
4. Total lymphoid irradiation
5. Thymic transplantation
6. Marrow treatment (in vitro)
   a. ATG + complement
   b. Monoclonal anti-T-cell antibody ± complement
   c. Monoclonal anti-T-cell antibody coupled with ricin
   d. E-rosette depletion
   e. Lectin separation
   f. Elutriation
   g. Immunoadsorbent column

[a]Data are from references *15, 21,* and *99.*

GVHD resembles a number of naturally occurring autoimmune collagen vascular diseases, including progressive systemic sclerosis, systemic lupus erythematosus, lichen planus, Sjögren's syndrome, eosinophilic fasciitis, rheumatoid arthritis, and primary biliary cirrhosis (*43*). The most frequent clinical feature of chronic GVHD is dermal involvement, which occurs in almost all (80%–90%) patients (*44,45*) (table 4). Erythema, dyspigmentation, poikiloderma, and lichenoid lesions that are observed, without therapy, can result in progressive induration and sclerosis that leads to joint contractures and disability. With earlier diagnosis and immunosuppressive therapy, the incidence of disabling scleroderma and contractures has fallen from 40%–50% to 5%–10% (*3,40*). Liver involvement is characterized as functional abnormalities evident as elevated liver enzymes, although hepatocellular dysfunction can make it difficult to distinguish chronic GVHD from viral hepatitis (*46*). Chronic GVHD may also involve other sites: oral (80% of cases), esophageal (13%), gastrointestinal (25%–35%), and ocular (80%–90%) (*6,44,47–49*). A syndrome of bronchodilator-resistant air flow obstruction resembling bronchiolitis obliterans has been described in patients with chronic GVHD (*50*). Less common are gynecological, muscular, serosal surface, and neurologic involvement (*51,52*).

Chronic GVHD is a clinicopathologic syndrome that requires correlation of clinical, histopathologic, and laboratory data (*53*) (table 5). Limited chronic GVHD is characterized as minimal organ involvement, such as localized skin disease or hepatic dysfunction. On the other hand, extensive disease presents as multiorgan involvement that usually includes skin, liver, oral, and ocular disease and several other potential target organs. Treatment of extensive chronic GVHD has led to complete arrest of disease in patients treated with a combination of prednisone and procarbazine, cyclophosphamide, or azathioprine (*3,6,44*). The average duration of treatment is 24 months, and by 4 years posttransplant 80% of patients are free of active GVHD and off immunosuppressive treatment (*44*). Other therapies that have been reported include the use of anti-T-cell immunotoxin (*54*) and a combination of photosensitizing drugs and ultraviolet A irradiation (*55,56*). Mortality associated with chronic GVHD is usually due to infection, with both the disease and therapy-induced immunosuppression significantly increasing susceptibility. Overall, prognosis is best with the limited form and less favorable with extensive chronic GVHD (*6*). The type of onset of chronic GVHD also appears to influence outcome, with chronic GVHD that progresses directly from acute GVHD being least favorable, onset that follows a quiescent period following acute GVHD being intermediate, and de novo onset chronic GVHD being most favorable (*57*). Acute GVHD prophylaxis appears to have no influence on the development of chronic GVHD (*58*). Attempts at preventing chronic GVHD by using immunosuppressive therapy have had disappointing results (*59,60*).

Table 4. Clinical manifestations of extensive chronic GVHD[a]

Manifestation	Incidence (%)
Dyspigmentation, erythema, scleroderma	80–98
Increased liver function	80–90
Oral mucositis and/or sicca	70–85
Ocular sicca	75–90
Joint contractures	40–50
Esophagitis	30–36
Serositis	20
Enteritis	18
Obliterative bronchiolitis	10–20
Interstitial pneumonia	8–28
Myositis	10
Bacterial infections	68
Weight loss	50
Karnofsky performance score (range): 40%–100%	

[a]Data are from references *6, 21,* and *65.*

Table 5. Clinicopathological classification of chronic GVHD[a]

Chronic GVHD type	Manifestation	Additional manifestations
Limited	Localized skin involvement and/or Liver dysfunction caused by GVHD	
Extensive	Generalized skin involvement; or	Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis; or
	Localized skin involvement and/or liver dysfunction due to chronic GVHD	Ocular involvement (Schirmer's test with <5 mm wetting; or Oral mucosal or minor salivary gland involvement demonstrated on labial mucosal biopsy; or Involvement of any other target organ

[a]Data are from reference *53.*

GRAFT-VERSUS-LEUKEMIA EFFECT

Early reports indicated that patients suffering from mild or no GVHD had an improved survival rate compared to those with more extensive disease (55% vs. 15%) (*61*). However, with the development of better supportive-care measures and improved management protocols for GVHD, one potential benefit of GVHD has become evident. It has been noted that leukemia patients who underwent allogeneic transplants and experienced GVHD had a significantly lower rate of leukemic relapse after BMT (*7,8*). A report by Sullivan et al. (*62*) showed that 48% of patients developing no or mild acute GVHD suffered leukemic relapse, while only 28% of patients developing grade II–IV acute GVHD had recurrence of leukemia; a similar relationship was shown for patients with chronic GVHD wherein 34% of patients with extensive chronic GVHD versus 45% of patients with no GVHD suffered leukemic relapse. The incidence of relapse for patients developing both acute and chronic GVHD was 28% compared to 52% for patients with no history of either acute or chronic GVHD who suffered relapse..

ORAL GRAFT-VERSUS-HOST DISEASE

Oral complications are frequently encountered in patients undergoing BMT. Over the last decade much has been learned about the oral complications associated with marrow transplantation (*56*). It is now clear that the type, timing, and severity of complications vary with several factors, including the patient's underlying disease and general health, conditioning regimens and their relative stomatotoxicity, incidence of oral infections, and the type and severity of acute and chronic GVHD (*56,63–67*).

Oral Acute Graft-Versus-Host Disease

Since there are several potential causes for oral mucosal changes during the first several months posttransplant, it has been difficult to distinguish those changes due to acute GVHD from those due to other causes. A review of the literature reveals mainly anecdotal or case reports or uncontrolled small-group reports available to detail the oral manifestations of acute GVHD. These reports have attributed to acute GVHD such changes as punctate or generalized mucosal erythema, white striae or papules on oral mucosa and lips (in patterns similar to those seen with oral lichen planus), mucosal erosion-desquamation-ulceration, mucoceles, partial or total xerostomia, and pain (*56,68–74*). However, many of these changes can also be caused by pretransplant chemoradiotherapy conditioning, posttransplant drugs such as MTX, or infections, and it is generally believed that it is difficult to differentiate the clinical oral manifestations of acute GVHD from those due to other causes, especially during the first several weeks post-BMT.

We undertook a series of studies to determine whether it was possible to differentiate the oral manifestations of acute GVHD from other oral complications based on clinical examinations. Kolbinson et al. (*75*) followed a group of patients sequentially, starting before transplant and extending to 5 weeks post-BMT; the pattern and types of clinical mucosal changes noted in the early post-BMT period (approximately days 0–14) indicated that the primary cause of mucosal breakdown (mucositis) was conditioning-regimen toxicity; the use of MTX to prevent GVHD can cause or contribute to mucosal damage (*75*), with other studies indicating similar results (*63,76–78*). Moreover, this is the period of highest incidence of oral herpes simplex virus infections in patients not treated prophylactically with acyclovir, the consequences of which can have a profound impact on oral tissues (*67*).

Subsequently, a study of 55 allogeneic transplant recipients was carried out to specifically determine the oral manifestations of acute GVHD (*64*). Eleven percent of patients developed grade I acute GVHD, and 27% had grade II–IV acute GVHD, with a median day of onset of 19 days post-BMT (range, 6–31). Hsaio et al. (*64*) found that the mucosal changes most frequently associated with acute GVHD were erythema and lichenoid changes; ulcerative, atrophic, and hyperkeratotic changes were less specific or less common. While most patients with acute GVHD complained of xerostomia, mucocele formation was not noted. Of significant importance was the finding that it was not until after day 21 post-BMT that trends clearly emerged that were significantly associated with acute GVHD, which is consistent with a report by Barrett and Bilous (*73*). This is not to say that acute GVHD does not cause oral lesions earlier, rather that it is unlikely that they can be differentiated from other toxic effects and infections. Not all areas of the mouth were equally involved, with the tongue and labial and buccal mucosa the most frequently involved sites. Other trends noted were that *(a)* herpes simplex virus-negative oral mucositis that persisted or worsened after day 21 post-BMT was suggestive of acute GVHD; *(b)* subjective pain and dryness tended to be worse in acute GVHD patients; pain and xerostomia that suddenly worsened 4–5 weeks post-BMT were suggestive of evolving acute GVHD; and inflamed minor salivary gland duct orifices were seen, but mucocele formation was not noted; and *(c)* erythema and lichenoid changes had the highest positive and negative predictive values for acute GVHD. Finally, it was concluded that the types and patterns of acute GVHD oral changes were consistent with those that have been reported for chronic GVHD (*65,73,79,80*).

Currently, the diagnosis of oral acute GVHD depends on the demonstration of systemic signs and symptoms of acute GVHD and the exclusion of other causes of oral lesions. Barrett and Bilous (*73*) have reported a group of five patients with acute GVHD in whom the oral manifestations of acute GVHD did not occur until between 3 and 31 days after the clinical onset of systemic acute GVHD. Review of data from the Fred Hutchinson Cancer Research Center, however, revealed several instances of probable oral acute GVHD changes that preceded the onset of skin rash and other systemic manifestations by as much as 5–6 days (*79*).

Only one study has looked to determine the histopathology of oral acute GVHD (*81*). This study concluded that the histopathologic criteria for both acute and chronic GVHD for oral mucosa and minor salivary glands were very similar (*81,82*). However, it was believed that the histological diagnosis of oral acute GVHD in the first several weeks post-BMT can be significantly hampered by the effects of conditioning regimens and infections (*82*). In addition, the risk of infection, hemorrhage, and pain can make it difficult to obtain biopsies in the first 4–6 weeks posttransplant. It is interesting that in a histopathologic study with a rat model for acute GVHD, Beschorner et al. (*83*) found that tongue mucosa and salivary glands exhibited changes directly analogous to those changes reported in humans and that the tongue was the earliest non-lymph node

site of acute GVHD injury and was the most sensitive nonlymphoid tissue for monitoring acute GVHD. This is especially interesting in light of observations reported by Kolbinson et al. (*75*) and Hsiao (*79*) that the tongue was one of the most frequent sites of mucositis or GVHD involvement, respectively.

With the lack of clearly defined criteria for diagnosing oral acute GVHD, it has not been possible to accurately determine the incidence rates for oral acute GVHD. The incidence rate for oral acute GVHD has been estimated to be between 33% and 75% for allogeneic transplant recipients (*70,71,73,75*). Among a series of 15 allogeneic patients, Barrett and Bilous (*73*) reported that seven subjects had oral and/or salivary gland acute GVHD involvement and four more had possible oral GVHD manifestations. This is consistent with the estimate from our study of an incidence rate of between 40% and 65% for patients with grade II–IV acute GVHD (*64,79*).

There are no reported clinical trials that have studied the prophylaxis or treatment of oral acute GVHD. Clearly, the best means of preventing or managing "oral" acute GVHD is the successful "systemic" prevention or management of disease. We have noted in uncontrolled trials that the topical application of steroid preparations appears to aid in reducing the severity and duration of acute GVHD oral mucositis pain and clinically diminishes the intensity of certain lesions, such as ulceration and lichenoid changes (*56*). An interesting technique for the treatment of severe skin and oral acute GVHD was reported by Atkinson et al. (*55*); a patient was successfully treated by administration of the photosensitizing drug psoralen, followed by skin and oral exposure to ultraviolet A irradiation.

It should also be noted that in patients with oral manifestations of acute GVHD, oral infections due to herpes simplex virus and *Candida* spp. can occur simultaneously, exacerbating the mucositis symptoms and making recognition of GVHD more difficult. Careful diagnosis and appropriate treatment can reduce the oral pain caused by these infections (*56*). Good oral hygiene and prevention of tissue trauma appear to be important.

Oral Chronic Graft-Versus-Host Disease

The oral manifestations of chronic GVHD have been well described (*56,65,66,72–74,80,84,85*). Generally, the oral changes ascribed to acute GVHD are clinically very similar to those originally attributed to chronic GVHD, although in the case of the latter they may be more readily recognized with the resolution of conditioning-regimen oral toxic effects and decreased risk of oral infections. We prospectively studied 60 long-term survivors, 27 with no history of chronic GVHD and 33 with active extensive chronic GVHD, to determine the oral manifestations of chronic GVHD (*65*) (table 6). The change most frequently associated with chronic GVHD was erythema. In patients with longer-standing disease, the erythema assumed a more telangiectatic pattern, a change that was supported by lip biopsy findings. Mucosal surfaces appeared clinically to be atrophic, which was attributed to a relative loss of keratinization or loss of surface structure (filiform papillae, gingival stippling, etc.) (*56,65*). When there was severe liver dysfunction with elevated bilirubin levels, the oral tissues had a marked icteric coloration and appeared yellowish orange. Lichen planus-like changes were the most distinctive oral change and had the highest positive predictive value (81%–100%). Hyperkeratotic striae, patches, plaques, and papules were noted to involve oral and perioral tissues; lichenoid changes varied from faint and patchy to heavy and confluent. Severe atrophy and ulceration consistent with erosive lichen planus were noted in patients with severe extensive chronic GVHD. The ulcerations were often covered with a heavy pseudomembranous clot that was greyish white to yellowish. Mucoceles and inflammation of salivary gland ducts were also noted, though not frequently enough to be significant. In patients displaying sclerodermatous GVHD changes, decreased oral opening due to perioral fibrosis was seen.

Table 6. Oral manifestations of chronic GVHD[a]

Manifestation	% of patients with manifestation
Mucosal erythema	52–73
Mucosal atrophy[b]	36–55
Lichenoid	30–36
Oral pain	56
Xerostomia (subjective)	52

[a] Data are from reference *65*.
[b] Clinical impression of mucosal thinning or loss of keratinization.

Subjectively, oral pain was often reported by patients with chronic GVHD and was either continuous or occurred on stimulation when eating or with the use of oral hygiene products. On review of patient histories, pain was often the first symptom associated with the onset of chronic GVHD or heralding a flare-up of disease (*65*). Subjective dryness has also been associated with chronic GVHD (*65,70*). In the first 4–6 months post-BMT, xerostomia due to chronic GVHD cannot be differentiated from radiation-induced salivary gland dysfunction (*65,86–88*), although a worsening of xerostomia can be associated with the onset or a flare-up of chronic GVHD.

While oral lesions are most common in patients with extensive chronic GVHD, patients in our and other centers have been described who have limited disease involving only the oral cavity (*56,89*). In addition, we have noted that the oral cavity can be the site of persistent activity after the resolution of chronic GVHD affecting other sites.

The presence of a Sjögren's-like syndrome following marrow transplantation was one of the earliest reported oral changes in patients with chronic GVHD (*85,90*). Keratoconjunctivitis sicca, salivary gland dysfunction, and histopatholgic changes consistent with Sjögren's syndrome are noted in patients with chronic GVHD. While subjective assessments of GVHD-associated xerostomia have been reported by a number of investigators (*70,72,74*), studies of salivary function by several authors have shown that decreased salivary flow rates due to chronic GVHD cannot be differentiated from those due to radiation for the first 4–9 months post-BMT (*84,86,91*). However, studies of patients 1 year or later after transplant have demonstrated that chronic GVHD does adversely influence salivary flow rates.

Izutsu et al. (*86–88,92,93*) have shown that chronic GVHD can cause increased concentrations of sodium, albumin, and IgG and decreased levels of secretory IgA and inorganic phosphate. The effect of GVHD therapy on salivary function must also be kept in mind; we have noted that with earlier detection and treatment of chronic GVHD, the incidence of subjective salivary gland involvement seems to decrease.

The histopathologic changes of oral mucosa with chronic GVHD have been characterized as a mononuclear cell infiltrate subepithelially with lymphocyte invasion and degeneration of the basal cell layer (*80–82*) (table 7). Ultrastructure studies by

Sale et al. (*94,95*) have demonstrated that the necrosis of epithelial cells is mediated directly by cytotoxic T-cells. With more intense involvement, severe atrophy and ulceration can result (*72,73,80*). Minor salivary gland involvement is initially characterized as a periductal lymphoplasmacytic inflammation, with subsequent infiltration and individual epithelial cell necrosis. Acinar damage and inflammation tend to occur later (*81*). An immunohistochemical study of oral lichen planus-like eruptions has shown infiltrating lymphocytes to be Leu-1^+ Leu-4^+ and express the phenotype associated with suppressor/cytotoxic T-cells (Leu-$2a^+$) (*96*). Keratinocytes expressing HLA-DR antigen were targeted and damaged by the Leu-2^+ cells. More recently, we have found that the lack of IgA-bearing lymphocytes in labial mucosa biopsies is significantly associated with the presence or future development of chronic GVHD (*97*).

Chronic GVHD develops in between 25% and 40% of long-term survivors of allogeneic BMT (*6*). The incidence of oral involvement has varied, with upwards of 80% of patients with extensive GVHD having some type of oral involvement (*6,65*). Oral examinations and labial mucosal biopsies obtained between 80 and 100 days post-BMT have proven to be useful in the overall assessment of patients for chronic GVHD (*81,97–100*). Individually, oral examinations and lip biopsies have been shown to have very high predictive values for extensive chronic GVHD. When the oral examination is positive, the predictive value for chronic GVHD based on a combination of oral examination results plus biopsy results approaches 100% (unpublished data).

The best management strategy for oral chronic GVHD centers on successful systemic therapy (*44,101,102*) (table 8). Attempts at using topical steroids have had mixed results, with relief of pain and irritation being much more likely than actual resolution of oral lesions. The use of a combination of the photosensitizing drug psoralen and ultraviolet A irradiation has been reported to have been useful in controlling oral chronic GVHD, but requires more study (*55*). The potential for oral overgrowth by *Candida* spp. or reactivation of herpes simplex virus in GVHD patients on immunosuppressive therapy must be kept in mind as a cause of (worsening) symptomatic mucositis. Finally, patients at risk for caries due to salivary gland dysfunction (xerostomia) will require fluoride or remineralization therapy.

CONCLUSIONS

Oral GVHD is a significant and unique complication of marrow transplantation. It is important that it be recognized and managed appropriately so that its impact on the course of recovery and ultimate survival of patients is minimal. There is significant need for research on all facets of oral GVHD—pathophysiology, diagnosis, and management.

Table 7. Oral histologic criteria for GVHD[a]

Grade	Squamous oral mucosa	Ducts of minor salivary glands
I ("consistent lesion")	Basal vacuolar degeneration with mononuclear infiltrates	Abnormal periductal mononuclear infiltrates
II ("diagnostic lesion")	Eosinophilic bodies	Ductal epithelial cell necrosis, often with dilation and attenuation or obliteration

[a]Data are from references *81* and *82*.

Table 8. Management strategies for oral GVHD[a]

Diagnosis	Correlation of systemic manifestations with oral changes
	Recognition of oral manifestations of GVHD
	Biopsy: labial mucosa, minor salivary gland
	Cultures (to rule out bacterial/fungal/viral lesions)
Treatment	
Oral lesions	Systemic immunosuppressive therapy
	Topical corticosteroids (rinses, gels, creams, etc.)
	Psoralen A plus ultraviolet A irradiation
	Antibiotics/antifungals/antivirals (as indicated)
	Topical anesthetics (short-term pain relief)
	Systemic analgesics
Xerostomia	Normal saline with sodium bicarbonate rinses
	Artifical salivas and oral wetting agents
	Cholinergic medications (e.g., pilocarpine, bethanechol)
	Lip-moisturizing agents (lip balms, lanolin, etc.)
Other	Daily topical fluorides (brush-on, rinses)
	Remineralizing solutions

[a]Taken from references *55, 56, 65,* and *81*.

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Osteoradionecrosis: Causes and Prevention

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Osteoradionecrosis (ORN) is one of the most serious complications arising from head and neck radiation therapy. Current research has shown that ORN represents nonhealing, dead bone and is not a state of infection. ORN is the result of functional and structural bony changes that may not be expressed for months or years. ORN may occur spontaneously or in response to wounding. Predisposing factors include absorbed radiation dose, fractionation, delivery modality, and dental status. Timing of dental extractions and other factors have also been shown to affect incidence. ORN may be reduced through early intraoral evaluation, treatment, and adequate healing time prior to beginning RT. Hyperbaric oxygen (HBO) therapy has been beneficial in the prevention and treatment of ORN. It is of paramount importance for the medical community to recognize the factors that may reduce ORN incidence, endorse oral care protocols, and acknowledge the value of HBO therapy in the prevention and treatment of this disease. [NCI Monogr 9:145–149, 1990]

Osteoradionecrosis (ORN), although not limited to the head and neck, is one of the most serious complications faced by clinicians in the management of patients who have undergone irradiation for head and neck tumors. Since ORN was first described in the 1920s, the causal and contributing agents and risk factors that predispose patients to susceptibility have been a topic of debate. For the past 50 years, clinicians have attempted to clarify statistics on the incidence of ORN. They have also studied contributing factors and offered suggestions to prevent or minimize its occurrence or severity. Finally, a variety of clinical guidelines for the management of ORN have evolved over the years.

Various authors have described ORN based on clinical findings, including exposed bone, nonhealing extraction sites, ulceration, intractable oral pain, and fistula formation. Later radiographic signs, including crestal bone irregularity, density changes, osteolysis, obvious sequestration, and frank pathologic fracture, have also been described.

The most common site of ORN is the mandible, with a few cases reported involving the maxilla. Neurologic involvement may occur along the path of the inferior alveolar nerve. Bone exposure and changes in local anatomy secondary to necrosis or surgical resection may compromise the patient's ability to maintain the area. Irritation of adjacent tissues is common. As necrosis continues, fistula formation (intraoral or extraoral), secondary infection, or pathological fracture may ensue. These may eventually lead to radical resection of the mandible and even patient mortality.

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The effects of ionizing radiation on bone and connective tissue are well documented and include suppressed osteoblastic activity, a decrease in cell numbers, disorganization of the bone remodeling apparatus, avascularity, and increased fibrosis (*1–8*).

On a cellular level, radiation produces early cell death through destruction of sensitive cell lines (epithelium, marrow, and tumor cells). In the process, cells of intermediate sensitivity such as bone, periosteum, connective tissue, and vascular endothelium undergo more gradual functional and structural changes that may not be expressed for months or years after irradiation. Damage of microvasculature accounts for much of the later effects seen in tissues related to ORN (*9*).

Descriptions of signs and symptoms of ORN often took the place of a concrete definition in much of the literature. Most authors are, to this day, forced to define the entity in terms of clinical parameters for their studies. Marx and Johnson (*9*) were critical in their assessment of authors who viewed minor soft tissue radionecrosis as ORN without proving actual bony involvement. They maintained that ORN represented true bone necrosis that usually existed with overt soft tissue necrosis. The entity represents not infected but nonhealing dead bone. They continued to define ORN as "an exposure of nonviable irradiated bone which fails to heal without intervention" (*9*).

The incidence of ORN has been reported in study samples of 20 to over 2,800 patients. The reported incidence ranged from under 2% to greater than 40%. Several recent studies show an incidence of under 15%, with widely divergent study populations (table 1).

Incidence reporting for ORN may not be as accurate as for other diseases due to the lack of a standard definition, lack of a simple confirmatory test for the presence of the condition, and the wide variety of participants examined under differing protocols for each study.

Early literature suggested that ORN was caused by high-dose irradiation in combination with trauma and infection. Trauma was usually the result of preirradiation or postirradiation tooth extraction, primary tumor excision, tumor-related surgical manipulation, or mucosal injury produced by an intraoral prosthesis. The traumatic incident was said to allow bacteria to enter the periosteum and bone, causing infection. Other modes of bone infection were thought to be related to dental caries and periapical and periodontal disease. Irradiated bone was thought to be susceptible to bacterial damage because of its inability to defend against invading pathogens due to decreased vascularity (*1,7,8,10–17*). The presence of the offending microorganisms and frank bone sepsis were not well demonstrated by culture or bone biopsy in early studies.

In 1983, Marx (*18*) performed microbial analysis on resected specimens from previously irradiated bone. The organisms found were compared to microorganisms readily isolated from nonirradiated specimens from areas of osteomyelitis (mandible, maxilla, and long bones) and infected bone grafts (jaws and long

Table 1. Incidence of ORN

Year	Author(s) (ref. No.)	No. of patients	No. (%) developing ORN
1938	Watson & Scarborough (*50*)	1,819	235 (12.9)
1940	Martin & Sugarbaker (*51*)	103	26 (25.2)
1953	Wildermuth & Cantril (*11*)	104	6 (5.8)
1958	Meyer (*52*)	491	26 (5.3)
1962	MacComb (*13*)	251	93 (37.1)
1962	Dodson (*53*)	108	10 (9.3)
1963	MacDougall et al. (*54*)	364	18 (4.9)
1966	Grant & Fletcher (*28*)	176	69 (39.2)
1967	Rahn & Drane (*55*)	120	53 (44.2)
1971	Rankow & Weissman (*44*)	176	12 (6.8)
1972	Wang (*56*)	262	15 (5.7)
1972	Beumer et al (*4*)	278	10 (3.6)
1973	Carl et al. (*57*)	47	2 (4.3)
1974	Cheng & Wang (*58*)	76	13 (17.1)
1974	Marciani & Plezia (*59*)	220	23 (10.5)
1976	Bedwinek et al. (*20*)	381	54 (14.4)
1980	Murray et al. (*8*)	404	77 (19.1
1981	Horiot et al (*16*)	528	10 (1.9)
1981	Morrish et al. (*19*)	100	22 (22.0)
1983	Beumer et al. (*23*)	72	16 (22.2)
1983	Larson et al. (*21*)	128	44 (34.4)
1983	Beumer et al. (*31*)	120	17 (14.0)
1983	Coffin (*60*)	2,853	22 (1.0)
1986	Archibald et al. (*33*)	22	3 (13.6)
1986	Marciani & Ownby (*37*)	109	3 (2.7)
1987	Epstein et al. (*32*)	1,000	26 (2.6)
1987	Schweiger (*25*)	324	6 (1.8)
1988	Kluth et al. (*26*)	135	14 (10.3)

bones). Microorganisms were absent from nonsurface areas of osteoradionecrotic bone. Marx concluded that ORN was a problem of wound healing rather than of infection. Trauma, sometimes linked to ORN by tooth removal, was not always a direct etiologic agent, but part of the pathologic process involving cellular death and collagen lysis, which places greater energy, oxygen, and metabolic demands on damaged tissue. He concluded by replacing the classic sequence of radiation, trauma, and infection with a sequence of radiation, hypoxic-hypovascular-hypocellular tissue, tissue breakdown, and nonhealing wounds as leading to ORN (*18*). This concept is most readily acceptable today, especially in light of current prevention and treatment studies.

The primary factor associated with ORN is radiation dose. Many authors have cited total irradiation doses greater than 65 grays as increasing the likelihood of ORN of the mandible, with higher doses greatly increasing the probability of ORN (*17,19–24*). Two authors recently found that high-dose radiation was not a factor in their cases (*25,26*). Dose is not the only radiation-related variable that has been proposed as contributing to ORN. The volume of the mandible included in the field (*6,22–24,27,28*) along with the proximity of maximal dosing to bone (*17,20–22,24*) have been shown to contribute to morbidity. Various authors have also shown that the type of radiation therapy (unilateral, bilateral, or external beam; interstitial; by carrier; or combination modalities) may contribute to ORN (*6,17,21*). This, however, is still related to the principle of total radiation dose delivered to bone (primarily mandible) and not to the calculated tumoricidal dose, as the dose absorbed by the tumor and the mandible may be quite different.

Clinicians realize that there is considerable variation among patients and that apparently similar individuals (i.e., in dental and oral status) treated for identically-staged tumors in the same anatomic location with the same therapy might have vastly different outcomes. This was best alluded to by Marx and Johnson (*9*), who discussed the fact that the energy absorbed per gram of tissue (gray) does not take into account tissue sensitivity, cellular mix, local tissue health, recent tissue insult, or patient systemic health. Dose rate may also play an important role in outcome, which may be one factor to account for the higher risk associated with interstitial delivery modes. Judgment of an individual's response to radiation therapy, to include varying degrees of the commonly accepted short- and long-term effects of ionizing radiation, may provide insight into the actual status of an individual's tissues. These physical signs should not be overlooked in evaluating the patient's risk of developing ORN along with total radiation dose, fraction rates, etc. (*9*).

The presence of teeth in the field of irradiation does represent an increased risk factor. This may be directly linked to preexisting dental disease involving the periodontium or periapical areas of the tooth. The potential for postirradiation trauma in dentulous areas related to dental or surgical manipulation does exist. Although an edentulous mandible does not preclude the development of ORN, studies have shown that the likelihood of ORN is decreased in edentulous persons, especially if they were edentulous before radiation therapy began (that is, did not receive multiple extractions in preparation for radiation therapy) (*17,19,22,29*).

Dental extractions have long been associated as a risk factor for ORN. In early studies they were considered a source of infection and trauma and, in more recent studies, part of the pathology associated with collagen lysis and induced cellular death. The timing of dental extractions in relation to the beginning or completion of radiation therapy has been studied by many authors, with a wide range of results. Preradiation extractions were shown to increase the potential for ORN compared to patients who did not require dental surgery (*6,12,20,24,30,31*). However, postradiation extractions, while not found to be a significant risk factor in one study, were shown by most authors to be the significant factor predisposing to ORN (*8,12,16,19,22–24*).

Those few who had success with postirradiation extractions in the early literature looked towards revascularization over time combined with excellent surgical technique as reasons for success. More recently, investigators have shown that revascularization does not occur and that the time elapsed between radiation therapy and tooth removal has little direct bearing on the occurrence of ORN (*22,23*). In fact, according to one recent study, the risk of ORN increases 6 months after radiation therapy and continues to increase with time as vascularity and tissue perfusion decrease and fibrosis increases (*9*).

The concept of spontaneous ORN has gained acceptance. These cases were first associated with higher irradiation doses, radiation sources closer to bone, and greater irradiated volume of bone (*4,17,20,24,32*). Spontaneous ORN occurs when no obvious etiology is found in either dentulous or edentulous segments. It is now thought to be caused by the destruction of a

great number of cells in "normal" tissue that cannot repair themselves after destruction by radiation. Tissues break down after initial hypervascularity and inflammation, passing through hypovascular and fibrotic stages into necrosis, usually within 2 years after radiation therapy (*9*).

Trauma-induced ORN has also been described. Early trauma-induced ORN occurs when surgical insult approximates radiation therapy. Late trauma-induced ORN occurs at a later time when trauma occurs, typically years after radiation therapy. The mechanisms of early and late trauma-induced ORN have been described to include cellular death associated with surgical wounding and poor recovery of irradiated tissues. Timing is related to the occurrence of the traumatic event. Marx and Johnson (*9*) have distinguished these in terms of two curves that depict radiation injury over time modified by the detrimental effects of trauma and the beneficial effects of hyperbaric oxygen therapy.

Periodontal disease has been viewed as a major predisposing factor associated with ORN, especially when the teeth involved remained in the field of irradiation (*24*). Some authors have linked poor preirradiation dental status with higher incidence of ORN (*24–26*). The presence of periodontally involved teeth increases the likelihood of postirradiation extractions, which, as mentioned earlier, are the major causes of trauma-induced ORN. Beumer et al. (*24*) found that bony exposures bounded by attached gingiva fared better than those that extended beyond the mucogingival junction. Use of removable partial or complete dentures has been linked to a number of ORN cases through the production of mucosal ulceration, which progresses to involve bone. These ulcerations may or may not be associated with recent extraction sites (*20,24,32*). Recommendations for the use of tissue-supported prosthesis vary from author to author. Good patient compliance, adequate saliva, and frequent examinations are all necessary to help preclude serious denture-related ulcers. Patients who have worn dentures for a long time prior to radiation therapy seem to be at substantially less risk of developing ORN than patients who have had pre- or postradiation extractions (*22,24*).

Finally, concurrent cancer chemotherapy has been examined as a potential cofactor in causing ORN. Treatment of head and neck tumors with irradiation and chemotherapy was not shown to increase the incidence of osteoradionecrosis (*33*). In another study (*26*), the authors cited methotrexate as a possible link to mucosal changes leading to ORN. This finding was not significant, however, due to the small number of patients in the study. These authors also noted a significant correlation between continued tobacco and alcohol use among their study group, which exhibited a higher incidence of ORN compared to controls (*26*).

Prevention of ORN has centered around the study of causal or associated factors related to its occurrence. As described in the literature and determined by clinical experience, certain steps can be taken to help decrease or minimize the incidence of ORN. It has become apparent that a certain number of cases will arise spontaneously in spite of the combined efforts of conscientious oncology team members.

The first step toward prevention of ORN is by thorough, early preradiation intraoral evaluation by the dental oncologist. Teeth with questionable prognosis, particularly those in the mandible within the field of irradiation, should be extracted. Teeth exhibiting furcation involvement, gross mobility, or periodontal disease should be removed, as should teeth with questionable pulpal status due to deep carious lesions or periapical pathology. Teeth in the field with a poor prognosis or those that would normally be extracted for prosthodontic reasons at some future date should be removed before radiation therapy begins.

Extractions should be performed with excellent surgical technique in conjunction with alveolectomy and primary closure, so as to speed healing and eliminate the potential for sharp bony edges or spicules, which may project into the overlying soft tissues (*1,22,24,34–37*).

Adequate healing time before radiation therapy begins is essential. Suggested healing intervals have ranged from as little as 10 days up to 25 days (*1,16,22,38*). One recent study has shown that removing teeth from segments 14 days before radiation still poses a risk for ORN. The risk was reduced to zero if there was a 21-day or greater interval between extraction and initiation of radiation therapy (*9*).

Extraction of teeth or wounding during radiation therapy will create an extremely high risk of ORN and is strongly discouraged. Removal of teeth from previously irradiated fields is also discouraged unless precautions are taken. These teeth should be maintained, if possible, through endodontic therapy with or without coronal recontouring (crown amputation). It has been shown that endodontic management of teeth in previously irradiated segments does not increase the incidence of ORN (*39*).

If extensive wounding or extraction in irradiated fields is necessary, then hyperbaric oxygen (HBO) treatment should be used both prior to surgery and after wounding. HBO has been shown to be more beneficial than conventional antibiotic prophylaxis [5.4% incidence of ORN versus 29.9% (*9,40*)].

Prevention of ORN is linked not only to removal of potential causal factors (teeth) prior to radiation, but also to maintenance of residual teeth and periodontium. To this end, preradiation scaling and root planing, prosthesis evaluation, oral hygiene instruction, topical fluoride carriers, and other intraoral preparations are advocated to prevent caries and periodontal problems that may lead to infection or tooth loss (*24,26,35,41*).

Use of dentures on irradiated tissues must be weighed carefully by the clinician. After the initial mucosal changes have subsided, factors such as patient compliance, aptitude, saliva quality and quantity, and the presence of recent extraction sites are parameters for making decisions about denture use (*20,24,29*). Avoidance of tissue-borne removable dentures for at-risk patients for whom absolute compliance is uncertain is probably warranted.

While tumoricidal doses of irradiation are often used without consideration for oral structures that may be adversely affected, the use of shielding devices may help to protect at-risk structures (bone, salivary glands, etc.). These may be constructed to shield or displace tissues that would otherwise receive incidental radiation, eliminating the chance of morbidity related to radiation-induced changes (*24,42*).

Treatment of ORN via the nonsurgical route prior to the use of HBO therapy consisted of improving local oral hygiene, avoiding local irritants like alcohol and tobacco, irrigation and packing with a variety of agents, systemic antibiotics, and pain medication (*32,43,44*). These techniques were sometimes accompanied by local debridement and removal of sequestered bone fragments, but often led to subtotal resections or mandibulectomy due to failure to control the disease process with

so-called conservative measures. Due to the greater oxygen and metabolic demand of irradiated bone and mucosa, delayed intervention may lead to greater destruction (*45*).

HBO therapy was shown to be an effective adjunctive treatment for ORN by Hart and Mainous in the mid-1970s (*46,47*). It was demonstrated to help cure ORN when combined with other measures. In persistent cases of ORN, surgical intervention became necessary (*32*). Marx (*45*) maintains that HBO must be used with aggressive surgical techniques to "save time" and spare morbidity in severe cases of ORN. He has recommended a progressive staging of cases depending on treatment outcomes (success or failure) from the beginning of therapy through the reconstructive phases. This staging concept was used to successfully treat 58 patients with HBO therapy and aggressive surgery, when needed (*45*). Soft tissue wound healing, enhanced osteogenesis, and fibroblastic stimulation followed by neovascularization are beyond the scope of this presentation (*45,48,49*).

In summary, ORN may develop due to spontaneous events of unknown etiology. Most often, ORN can be linked to postirradiation wounding, usually associated with a surgical event (extraction), preexisting dental disease remaining in the fields of irradiation, or breakdown of a preirradiation extraction site. Secondary surgeries related to tumor control and denture-related ulcers have been identified as lesser causes of ORN.

In light of the evidence reviewed for the preirradiation management of the oral cavity and postirradition use of HBO therapy, the vast majority of ORN cases should be preventable. One factor that continually arises in clinical practice is the ongoing discussion between dental and radiation oncologists about delaying radiation therapy to permit an ideal healing interval for preirradiation extraction sites. An open dialogue between professionals should evolve an acceptable consensus on this issue. While the primary aim of the radiation oncologist is tumor cure, ORN is a serious potential outcome of therapy and should not be discounted. A prospective study of delay in instituting radiation therapy to achieve extraction site healing, incidence of ORN, and success or failure in achieving a cure of the primary tumor should be undertaken.

The larger issue of preradiation oral evaluation for head and neck cancer patients must be emphasized throughout the medical community, along with timely preirradiation care and third-party reimbursement for dental providers.

HBO therapy is being recognized as the treatment of choice for high-dose irradiation patients who require extractions or wounding in previously irradiated segments. Its validity must be endorsed or disproved through carefully controlled clinical studies. Furthermore, it is incumbent upon our health care delivery system to make HBO more widely available.

While the concepts of the pathophysiology, prevention, and treatment of ORN have changed over the past decade, few prospective clinical trials have been reported (*40*). Since the incidence of ORN is relatively low, multicenter trials to further improve preventive HBO regimens and continued exploration of other modalities should be initiated. These studies should analyze the financial impact of prophylactic HBO therapy on health care costs. Based on the studies cited, the incidence and morbidity of ORN can be reduced to improve the longevity and quality of life for at-risk head and neck cancer patients.

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Use of Hyperbaric Oxygen in Postradiation Head and Neck Surgery

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Data are presented to indicate the value of hyperbaric oxygen in all stages of treatment of patients with irradiation complications following head and neck surgery. Hyperbaric oxygen stimulates angiogenesis, with increased neovascularization and optimization of cellular levels of oxygen for osteoblast and fibroblast proliferation, collagen formation, and support of ingrowing blood vessels. The hypoxic, acellular matrix in the postirradiated field is changed to a hypercellular, hyperoxic/normoxic situation. Oxygen is used as an adjunct to appropriate surgery. By using the two modalities together, the salvage rate for osteoradionecrosis and its complications of orocutaneous fistula, pathological fractures, and severe bone losses can be increased dramatically. It may also be used prophylactically in patients with periodontal disease or teeth requiring extraction in a previously irradiated area. Finally, the use of oxygen helps support tissue flaps and grafts placed into previously irradiated areas. Economically, there is considerable cost savings in the use of hyperbaric oxygen therapy with appropriate surgery. From the patient's point of view, pain relief is achieved, function is returned, and prognosis improves in a relatively short time. [NCI Monogr 9:151–157,1990]

From the Hyperbaric Registry maintained at the Maryland Institute for Emergency Medical Services Systems (MIEMSS), we have been able to track the treatment profiles of patients with various conditions since 1970. The registry was developed by sending a yearly questionnaire to all known hyperbaric oxygen facilities within the country. A 53% response (130 of 245) was achieved by sending second and third questionnaires to those facilities not responding to the first mailing. Table 1 indicates the total number of patients in the registry who were treated during certain periods. In the first 7 years, roughly 1,100 patients with a very wide range of conditions were treated nationally each year. Approximately 70% of all conditions treated were in the accepted category described by the Undersea and Hyperbaric Medical Society Committee on Hyperbaric Medicine (*1,2*). Between 1978 and 1980, the number of cases treated increased to 2,200 per year. The most dramatic increase occurred from 1981 to 1989, during which time more than 6,600 patients were treated each year. This dramatic increase corresponded to wider dissemination of the knowledge of and rationale for the use of hyperbaric oxygen therapy and reflected a large increase in the number of monoplace (single-person) chambers.

The number of monoplace chambers increased because these chambers are significantly less expensive (approximately $80,000 each complete, with all fixtures) than multiplace chambers (approximately $400,000 each complete). Table 2 lists the number of patients treated in each type of chamber. Many of the multiplace chambers listed in the registry are located in facilities of the armed services, namely the Navy and Air Force, and are reserved for patients with decompression sickness and air embolism from deep sea diving or high-altitude flight. Oil industry regulations state that a hyperbaric oxygen facility must be available on the scene during underwater deep sea diving activities. Again, the commercial field use of hyperbaric oxygen facilities relates specifically to decompression sickness and air embolism treatments; the statistics from this type of operation are not available for public use. Such operations also represent an extremely narrow use of hyperbaric oxygen therapy. In addition, the actual number of patients is relatively small.

A number of hyperbaric oxygen facilities are available in the United States and Canada (fig. 1). In general, coastal states have more facilities, related to scuba diving and other water activity. Certain states within the midportion of the country do not have any facilities. It is evident that in today's world of rapid travel, we are not far from a hyperbaric oxygen facility at any location in the country. Persons may be transported to and from chambers by land transportation, helicopters, and fixed-wing aircraft. The registry at MIEMSS [(301) 328-7814] and a similar registry maintained by the Diver's Alert Network, Duke University, Durham, NC [(919) 684-8111], are available for public use and can direct inquirers to the nearest local chamber. The first survey of hyperbaric oxygen facilities in the country was done in 1977 (*3*) and showed that there were 37 functional facilities nationwide. Today that number has increased to 245 and has shown a steady, continuous rise over the last 3 years.

The steady increase in the use of hyperbaric oxygen for radiation-induced conditions such as radiation necrosis, unspecified osteoradionecrosis of the mandible and maxilla, soft tissue radiation necrosis, and radiation necrosis related to dental caries has been documented through the registry. Table 3 shows the number of people treated yearly for these conditions in the United States. The exact number of people treated in the whole country is not known because of the 47% that did not respond to the questionnaires. Other facilities are known to be treating patients, as determined by telephone calls, but the facilities have not responded to repeated questionnaires asking for their statistics.

MECHANISMS OF ACTION

Pressure and Basic Physics

The use of increased pressure and the exchanging of air with 21% oxygen for air of 100% oxygen as the breathing agent result in a greatly increased amount of oxygen being available to the

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Table 1. Number of patients treated, 1970-1989

Period	No. of yr in period	No. of patients treated
1970-1977	8	7,800
1978-1980	3	6,500
1981-1989	9	66,669

Table 2. Number of patients treated in monoplace and multiplace chambers, 1981-1988

Type of chamber	No. of institutions	No. of patients treated
Monoplace	151	42,972
Multiplace	78	14,575
Both	21	9,122
Total	250	66,669

tissue. This is due to the gaseous/fluid (oxygen/plasma) interphase that enhances oxygen absorption and transportation into the liquid phase of the blood. This greatly enhanced transportation of oxygen via the bloodstream is the result of numerous basic physics laws.

Pressure Laws

Pressure (unit force per area) has various units of measurement. The most commonly used is feet of sea water. One atmosphere of absolute pressure is equal to 33 feet of sea water (760 mm Hg). Gases are compressible, but body tissues, which are composed mainly of fluid (water), are not compressible and thus are not affected by pressure changes.

Gas Laws

Boyle's Law relates volumes and pressures. Pressure and volume are inversely proportional at constant temperature: $P_1V_1 = P_2V_2$, where P = pressure, V = volume, and 1 and 2 represent the different pressures and volumes.

Dalton's Law states that the total pressure of a mixture of gases is equal to the sum of the partial pressures of all of the component gases: $P(t) = P(O_2) + P(N_2) + P(X)$, where $P(t)$ = total pressure, $P(O_2)$, = oxygen partial pressure, $P(N_2)$ = nitrogen partial pressure, and $P(X)$ = partial pressure of remaining gases. The partial pressures of the gases change in proportion to the ambient pressure. The concentration of each gas remains the same.

Henry's Law states that the amount of any given gas that dissolves in a liquid at a given temperature is the function of the partial pressure of the gas and the solubility coefficent of the gas in the particular liquid: $\%Y = P(Y)/P(t) \times 100$, where $\%Y$ = amount of gas dissolved in the liquid, $P(Y)$ = partial pressure of

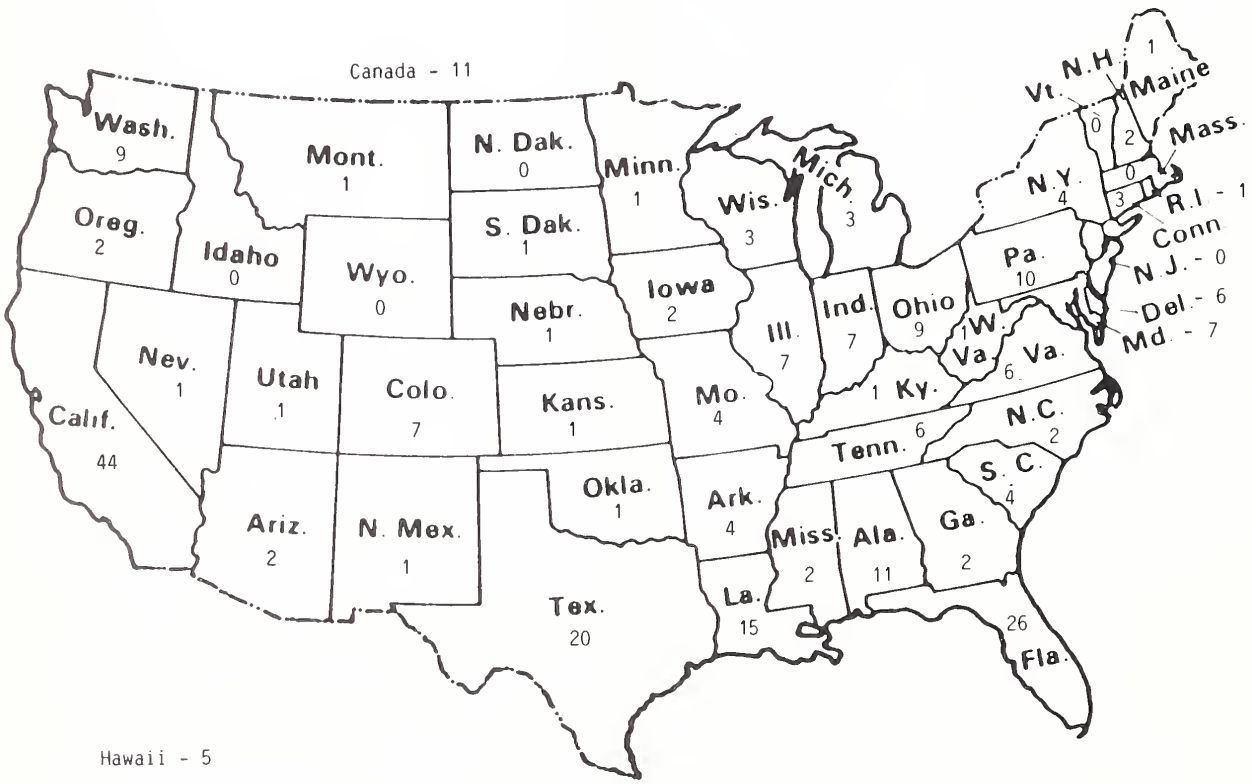

Figure 1. Map showing numbers of functional chambers in the United States and Canada as of August 30, 1989.

Table 3. Head-and-neck-radiation-induced conditions treated with hyperbaric oxygen therapy

Radiation necrosis type	No. of patients treated							
	1981	1982	1983	1984	1985	1986	1987	1988
General	189	129	112	89	178	155	185	88
Jaw	0	123	270	397	519	481	338	305
Soft tissue	217	177	138	181	185	136	195	170
Teeth	53	44	27	70	96	56	21	31
Total	459	473	547	737	978	828	739	594

the gas, and $P(t)$ = total atmospheric pressure. Very high concentrations of oxygen become dissolved in the plasma and are transported to the tissues, elevating oxygen levels in all areas of the body.

Oxygen and Wound Healing

Bullough and Johnson (*4*) demonstrated acceleration in the repair of wounds following hyperbaric oxygen therapy; mitotic activity increased in the epidermis as a result of increased oxygenation in the area. A similar increase in bone healing in animals has been demonstrated under hyperbaric oxygen conditions (*5–7*). It has been postulated by Chvapil et al. (*8*) that an atmosphere of alternating hypoxia and hyperoxia results in greater collagen synthesis. Their experiments showed that a larger amount of collagen was produced in wounded animals with alternating hypoxic and hyperoxic conditions than at normal atmospheric pressure. The intermittence of hyperbaric oxygen provides the hyperoxic-hypoxic stimulus for wound healing. Neovascularization plays an important role in wound healing; the dead space between the tissues is filled by new tissue. Collagen support is essential for ingrowth, and the new blood vessels are unable to extend across the dead space without the collagen support. Cells and collagen thus precede new capillaries. Hunt and Pai (*9*) postulated that the steep oxygen gradient stimulates the cells that are most distal from the capillary, resulting in rapid multiplication. Cellular migration occurs from the last capillary because of the high oxygen concentration. As capillaries bud into the area, further oxygen supplies are brought with them, and thus the cycle of hyperoxia and hypoxia continues, with further cycles of new capillary arcades being established. The vascular supply migrates more rapidly with higher oxygen levels; therefore, the rate of wound healing and defect closure is more rapid (*9*).

Neovascularization

Ketchum et al. (*10*) and Manson et al. (*11*) showed that new blood vessels develop as a consequence of hyperbaric oxygen treatments. The model used by Ketchum et al. (*10*) was the scalded backs of guinea pigs. A microangiographic technique demonstrated greater numbers of new blood vessels developing in animals subjected to hyperbaric oxygen following the burns than in the control animals not subjected to hyperbaric oxygen. Manson et al. (*11*) used the guinea pig model of a skin flap with the base-to-length of pedicle ratio that was inadequate to support the full length of the flap. Adenine triphosphatase (ATPase) staining in the tissue flaps showed significantly increased neovascularization and salvage of flap length in the hyperbaric oxygen-treated animal flaps compared with controls. Histochemical staining techniques showed that the lactate levels were reduced and the glucose levels were elevated further along the length of the tissue flap in the treated flaps compared with the control animal flaps. Hyperbaric oxygen is thus able to return the tissue oxygen level to a more physiologic one that supports both cellular and capillary proliferation. Further evidence of increased neovascularization is evident in the work of Mansfield et al. (*12*), Marx (*13*), and Greenwood and Gilchrist (*14*), in which this principle was applied to the treatment and healing of patients with osteoradionecrosis. The endarteritis obliterans caused by radiation therapy results in markedly reduced cellular stroma because of hypoxia.

Radiation-induced problems occurring in head and neck surgery have been for many years the nightmare of the reconstructive surgeon. Once developed, they are extremely difficult to manage. The complication rate ranges from 40% to 81%, and the subsequent success rate of reconstruction ranges between 20% and 65% (*15–16*). When disease develops in soft tissue or bone necrosis occurs, pain, disability, and progression are seen. As a consequence of tissue breakdown and loss of protective barriers (e.g., erosion of the carotid artery), death may also occur (*17*). Even if overt clinical disease does not develop, there may be latent radiation damage to tissue. Surgery or trauma to the area increases the risk of infection and wound dehiscence as well as tissue, graft, or flap loss (*18,19*). Wound dehiscence may occur early or even months after radiation. Exposed bone or graft in an irradiated area fails to vascularize and develop granulation tissue, with secondary infection and dehydration leading to complete graft loss. When a bone graft develops an infection, it is usually unresponsive to antibiotics or conservative debridement because of the hypovascular tissue bed. To resolve the infection, the bone graft must be removed. Late graft reabsorption is related to the cellular density of the transplanted graft material and the vascular density of the host recipient tissue. Here, if the cellular density remains high, the graft is retained; however, late reabsorption occurs in hypocellular recipient tissue, which is incapable of providing the osteogenic potential and of forming periosteum about the graft. Pathologic fractures may also occur any time between 6 weeks and 6 months postradiation, the result of the reduced number of transplanted osteocompetent cells as well as mineral matrix reabsorption and poor host-derived bone formation. Graft weakening is followed by fracturing.

The failure of the host tissues to support the graft is the major factor in failed jaw reconstruction in radiated tissue. Radiation produces a hypocellular-hypovascular-hypoxic tissue bed that is incapable of regenerating supportive vessels (*20,21*). The collagen is essentially mummified, and there are very few viable

fibroblasts or endothelium-lined vascular channels. Oxygen measurements in the area are 20%–30% of those of nonirradiated tissues. The hypovascular-hypocellular-hypoxic tissue is produced by the progressive, obliterative endarteritis caused by radiation.

Angiogenesis and Fibroplasia

Hyperbaric-oxygen-induced angiogenesis and fibroplasia have been studied by sequential biopsies and transcutaneous monitoring (*20–22*). Transcutaneous oxygen (TcO_2) records of patients in a resting state breathing room air were undertaken at two sites: one in the center of the radiation field, and the second in nonirradiated tissue. The left intercostal space (LSICS) is traditionally used for this reference. Measurements were taken daily for 52 patients breathing sea-level air. These individuals were also undergoing hyperbaric oxygen treatment later in the day. By normalizing the value of each patient's first resting measurement in the nonirradiated area to the number of hyperbaric oxygen exposures, a steady increase in transcutaneous oxygen in the irradiated area was seen, but there was no change over the reference area. It is believed that this represents an index of capillary density increase subsequent to neovascularization. Normal tissue is unaffected by hyperbaric oxygen.

Plotting these measurements produces an S-shaped curve (fig. 2) that has three phases: lag, rapid rise, and plateau.

The lag phase shows no measurable angiogenesis but reflects capillary budding and collagen synthesis. Tissue oxygen levels remain unchanged and are 30% ± 5% of the level in nonirradiated tissue until the eighth hyperbaric oxygen exposure.

The rapid-rise phase shows an increase to 82% ± 4% of the nonirradiated-tissue level between the exposures 18 and 23. The geometric rise is due to capillary budding from preexisting vessels in adjacent tissues. Neovascularization is accomplished, converting the hypovascular tissue to a more vascular tissue. Fibroplasia is more apparent, collagen production is more organized, and more cells are present.

In the plateau phase, the transcutaneous oxygen measurement levels off at 80%–85% of the level in nonirradiated tissue. Here, maximum angiogenesis has occurred, correcting tissue hypoxia. With the reduction of the number of lactate and hydrogen ions, the stimulus for angiogenesis is removed. In essence, the healing phase has been completed.

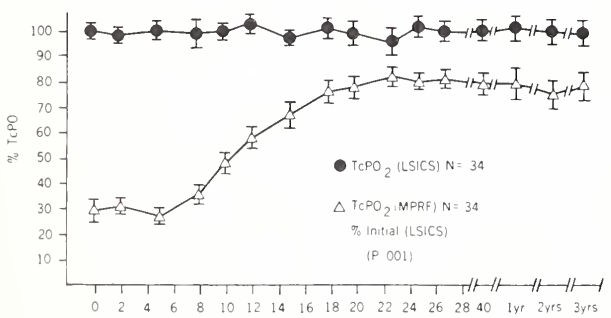

Figure 2. Changes in vascular density [measured by transcutaneous oxygen ($TcPO_2$) recordings at the left intercostal space (LSICS) and at the center of the irradiated area (MRPF)] of irradiated tissue as a function of hyperbaric oxygen exposures. Horizontal scale is marked in months and years. $P = .001$ for irradiated vs. nonirradiated tissue.

This angiogenesis has been shown to be long lasting by long-term follow-up of the plateau phase. Repeat measurements made between 1 and 4 years after hyperbaric oxygen exposure have shown that the transcutaneous oxygen values remain elevated.

A second study by Marx (*22*) duplicated the first, but additional points were measured throughout the irradiated tissue rather than only the central point. The center was documented as being overtly hypoxic. Gradually increasing levels of tissue oxygenation were noted moving outward through the peripheral and nonirradiated areas. A large oxygen gradient had been established from the periphery to the central region. At the periphery, levels of 40–45 mm Hg of oxygen were measured, whereas in the center the level was 5–10 mm Hg.

Knighton et al. (*23*) identified this high oxygen gradient as the driving force of normal wound healing through the release of angiogenesis factor by macrophages. Hyperbaric oxygen appears to allow the wound to develop steep oxygen gradients and changes the low oxygen gradients that resulted in low tissue perfusion levels. The ingrowth of new vessels thus is a major factor in the healing of these wounds. The end stage of healing is evidenced by a shallow oxygen gradient, even after hyperbaric oxygen exposures, with reduction in the macrophage-derived growth and angiogenesis factors. This is then the established plateau phase.

THERAPEUTIC USE

In the early management of patients, hyperbaric oxygen was administered alone without appropriate aggressive surgical debridement and removal of necrotic tissue. The net result was that the wounds appeared to heal and then broke down again, requiring repetitive hyperbaric oxygen treatment. Rankow and Weissman (*24*) defined this type of nonresponder as having continuously unresolved exposed bone after 1 year of treatment. Twenty-five percent of their patients were given this conservative therapy, which included irrigation with agents ranging from saline to hydrogen peroxide to 9-NH_2 acridine, and antibiotics, superficial sequestrectomies, and avoidance of local irritants. The rationale for this approach was the belief that osteoradionecrosis reflected primarily an infection in compromised bone.

Marx (*22*) saw a higher percentage of nonresponders (92%) in a group of 112 patients on a 1-year trial following the Rankow and Weissman (*24*) protocol. He showed that the costs of penicillin, tetracycline, oxycodone, codeine, outpatient visits, and inpatient days averaged together resulted in a 1-year expenditure (in 1985 dollars) of $28,400 per patient. In addition, many of the patients became addicted to the narcotics, 60% of them had continuous pain, and all lost a tremendous loss of time from family and workplace. Ultimately, partial jaw resection was undertaken and no hope of reconstruction was considered.

Reports of hyperbaric oxygen benefits began appearing in the literature in the 1970s (*25–28*). The surmise was that the effect of high oxygen was bacteriocidal or bacteriostatic (*19*). Hyperbaric oxygen was thus used as an adjunct to conservative therapy.

Marx's review in 1978 indicated that 26% of the hyperbaric-oxygen-treated patients had healed over their exposed bone;

however, half had a recurrence within 2 years, resulting in further exposure of nonviable bone. Similar experiences were reported elsewhere (*29*), with the resultant suggestion of 6 monthly retreatments with hyperbaric oxygen. In essence, the high cost and poor resolution rate made physicians feel that hyperbaric oxygen had little to add in alleviating their patients' misery.

In 1979, the work of Marx and others (*20,22,29*) began shedding light on the fact that an osteoradionecrosis wound-healing defect was related to chronic hypoxia rather than infection. A protocol was developed that combined hyperbaric oxygen with specific surgery as indicated. The patient's response or nonresponse to hyperbaric oxygen therapy became the main indicator for surgery. Dead bone was distinguished from compromised bone, and then all dead bone was resected surgically and wound healing was enhanced with hyperbaric oxygen therapies. Preoperative hyperbaric oxygen therapy stimulated angiogenesis and fibroplasia; thus, when ultimate bony reconstruction was required, the recipient site was prepared. The Marx protocol for osteoradionecrosis was established at the University of Miami and is summarized as follows.

Stage I. The presence of exposed bone in the region of radiation therapy for 6 months with or without pain was considered essential for the diagnosis of osteoradionecrosis. Stage I patients were those with active osteoradionecrosis without pathologic fracture, a cutaneous fistula, or radiographic evidence of bone reabsorption to the inferior border. Each patient received 30 hyperbaric oxygen exposures at 2.4 absolute atmospheres (ATA) for 90 minutes each time. Wounds were irrigated with saline, and no bone was removed. Antibiotics were discontinued, and at the end of 30 exposures, the wound was reexamined. A decrease in the amount of exposed bone, reabsorption, or spontaneous sequestration of exposed bone or softening of the exposed bone was considered clinical improvement. The patient was given a further 10 exposures to complete a 40-exposure course for full mucosal coverage. If no improvement was evidenced or if exposure of bone, no mucosal proliferation, or inflammation continued, the patient was considered a nonresponder and advanced to stage II.

Stage II. For patients not responding to the treatment in stage I, local debridement was undertaken to identify those with cortical or superficial bone involvement. A transalveolar sequestrectomy was done, the labial and lingual mucoperiosteal flaps being closed in three layers over a base of bleeding bone. Hyperbaric oxygen was continued for a total of 10 additional treatments. If wound dehiscence occurred with exposed nonhealing bone, the patient was then identified as a nonresponder and advanced to stage III.

Stage III. Nonresponders from stage II and those presenting with an orocutaneous fistula, a pathologic fracture, or radiographic evidence of bone reabsorption to the inferior border constituted stage III patients. Following the initial 30 treatments, the overt dead bone was resected via the transoral route. Tetracycline fluorescence under ultraviolet light was used to identify the viable end of the bone. External fixation of the mandibular segments was undertaken, and orocutaneous fistula or large soft tissue losses were closed or reconstructed at this stage. A further 10 hyperbaric oxygen treatments were then given, and the patient was advanced to stage IIIR.

Stage IIIR. Patients who completed stage III or who had primary resections followed by radiation were considered stage IIIR. Ten weeks after resection, the soft tissues were healed, so that the patient has a potential graft recipient bed free of infection. Transcutaneous oxygen measurements reflect 80%–85% revascularization of soft tissue. A transcutaneous bony reconstruction is performed; oral contamination is carefully avoided. Ten postreconstructive hyperbaric oxygen treatments are given, with the mandibular fixation maintained for a further 8 weeks. One month after fixation is released, full prosthetic rehabilitation can begin. If additional surgery to the soft tissues is required, it is performed after the fixation is released. The patient is then referred for maxillofacial prosthodontic work.

Resolution criteria are freedom from pain, retention or reconstruction of mandibular continuity, restoration of mandibular function, the ability to wear dental appliances if required, and, finally, the maintenance of intact mucosa and skin over the bone.

Among Marx and Johnson's 268 patients (*33*), 38 were at stage I, 48 were at stage II, and 182 were at stage III. Disease was resolved in all 268 patients following this protocol. A cost analysis of osteoradionecrosis in 300 patients was undertaken by Marx and Johnson (*33*) in July 1985, reflecting 1985 dollars. The results are presented in table 4.

Osteoradionecrosis Prevention

Roughly 35% of osteoradionecrosis occurs spontaneously with soft tissue breakdown over nonviable bone. Trauma such as tooth removal, biopsies, or placement of dental appliances initiates the other 65%. The clinician faces a dilemma when a patient requires dental care, oral biopsy, or extraction of teeth in an irradiated area. If the periodontal disease is untreated or the affected teeth are not removed, osteoradionecrosis may be initiated.

Seventy-four high-risk irradiated patients in need of dental surgery were selected for a study (*30*); each had received at least 6,800 rads to the mandible. In the penicillin control group, 11 patients (29.9%) developed osteoradionecrosis, whereas only two patients (5.4%) in the hyperbaric oxygen-treated group developed it (table 5). Eight of the 11 patients who developed osteoradionecrosis in the antibiotic group were then treated with the stage III hyperbaric oxygen–resection protocol to resolve their disease, and the other three were treated successfully with the stage II sequestrectomy protocol. The two patients who developed osteoradionecrosis in the hyperbaric oxygen-treated group responded to continued treatment following the stage II hyperbaric oxygen–sequestrectomy protocol.

Table 4. Cost analysis of osteoradionecrosis[a]

Treatment[b]	No. of patients	Avg 1-yr cost	Avg total cost	Resolution rate (%)
Non-HBO	65	$31,000	$102,000	8
HBO without surgery	51	$20,000	$82,000	17
Marx-WHMC protocol	130	$35,000	$35,000	100
Marx-WHMC protocol in private practice	54	$32,000	$32,000	100

[a] From Marx and Johnson (*33*).

[b] HBO = hyperbaric oxygen, WHMC = Wilford Hall U.S. Air Force Medical Center.

Table 5. Incidence of osteoradionecrosis following tooth removal in irradiated patients (≥6,800 rad)[a]

Group	No. of patients	No. of teeth	No. (%) of sockets with ORN[b]	No. (%) of patients with ORN
Penicillin	37	135	31 (22.9)	11 (29.9)
Hyperbaric oxygen	37	136	4 (2.6)	2 (5.4)

[a] From Marx et al. (*30*). © 1985, American Dental Association. Used with permission.
[b] ORN = osteoradionecrosis.

From these results, it is postulated that the angiogenesis and fibroplasia that occur as a result of hyperbaric oxygen therapy were able to enhance the healing potential in irradiated compromised tissues. This then allows the use of hyperbaric oxygen as prophylactic therapy for the prevention of osteoradionecrosis in patients with previously irradiated mandibles.

Greenwood and Gilchrist (*14*) demonstrated the effectiveness of hyperbaric oxygen in reducing the extent of ischemic necrosis in skin flaps in previously irradiated rats. At 5–7 months after exposure to 2,600 rads from a 150-kV X-ray machine, a rectangular full-thickness skin flap (6 by 4 cm) was raised. This was then sutured back to the animal. In the air-breathing controls (nine animals), the mean percent flap necrosis was 35%, whereas in the animals treated with hyperbaric oxygen at 2.0 ATA for 2 hours twice daily, flap necrosis averaged only 14%.

An increase in the success rate for bone grafts to irradiated tissues was sought in a randomized prospective human trial involving 104 patients (*14*). Following exposure to 6,400 rads or more, the patients were randomized into air-breathing control groups and groups treated with hyperbaric oxygen at 2.4 ATA for 90 minutes daily for 20 sessions. A complication rate of 11% and success rate of 92% were found in the hyperbaric oxygen group, compared with a complication rate of 26% and a success rate of 66% in the control group. The same technique and surgeon were used for all patients. The effect of the hyperbaric oxygen was to prepare the vascular and cellular tissues within the radiated bed, facilitating successive debridement and later reconstruction (*14,18,31,32*).

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Management of Salivary Dysfunction

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Xerostomia is a common complication of radiation therapy to the head and neck. In such cases, the symptom is often permanent and leads to difficulty in mastication, wearing dentures, deglutition, and speaking. Other side effects include candidiasis and caries. Therapy is for the most part symptomatic and empirical. However, the use of sialogogues shows promise. Effective salivary substitutes and sialogogues that have minimal side effects need to be developed. [NCI Monogr 9:159–161, 1990]

Many patients with malignancies of the head and neck undergo radiation therapy, either as the only method of treatment or in combination with surgery, chemotherapy, or both (*1*). Xerostomia is a common side effect experienced by almost all patients who undergo radiation therapy (*2*). Studies of experimental animals have shown that radiation causes atrophy of secretory cells and that the serous cells are more affected (*3*). Other studies, however, have suggested that the damage may be related to vascular impairment and changes in the connective tissue (*4,5*).

The consequent xerostomia is usually severe and often permanent, although some recovery of function has been reported. Many clinical problems ensue, including difficulty in chewing, swallowing, talking, and inability to wear dentures comfortably. Salivary dysfunction presumably permits colonization of the oral mucosa by opportunistic pathogens such as *Candida* spp., leading to candidiasis and invasion of tooth structure, often causing rampant caries.

Current therapy for chronic xerostomia includes the use of salivary substitutes or salivary stimulants. Water, glycerin preparations, and artificial saliva are used as substitutes for saliva, while pharmaceutical sialogogues, sugarless candies, and chewing gum stimulate saliva production (*6*). Sialogogues require functional salivary gland parenchyma in order to be effective. Although a significant proportion of the salivary glands may be included in the radiation fields, it is rare that all the minor and major glands will be totally compromised by the radiation therapy.

Some patients experience temporary relief of symptoms with artificial saliva. To be effective, the artificial saliva should be in a form that will relieve discomfort, provide lubrication, be long-lasting, inhibit the overgrowth and colonization of oral microflora, and induce rehardening of softened enamel. Levine and colleagues (*6*) list the possible constituents of artificial saliva as carboxymethylcellulose, mucins, sorbitol or xylitol, mineral salts, fluorides, and preservatives.

Studies have investigated whether artificial salivas containing carboxymethylcellulose are more effective than agents containing mucin, water, or glycerin. Matzker and Schreiber (*7*) administered a carboxymethylcellulose preparation to patients with chronic xerostomia; all who used it reported symptomatic improvement. S'Gravenmade et al. (*8*) gave a mucin-based preparation to a group of patients who had not liked the carboxymethylcellulose saliva; again the results were measured symptomatically, and the mucin-based preparation was preferred. Shannon and colleagues (*9,10*) used VA-Oralube, a carboxymethylcellulose preparation containing fluoride, in a group of 22 patients with radiation-induced xerostomia; they reported relief, and further studies with this preparation suggested that it was a well-tolerated and useful product.

Some products containing mucin are not available in the United States but have been reported to have better wetting characteristics. A recent double-blinded cross-over study by Visch's group (*11*) compared a mucin-based and a carboxymethylcellulose artificial saliva in patients with Sjögren's syndrome, chronic xerostomia, and postradiation xerostomia. The mucin-based preparation was preferred by all the patients, but more of the patients with postradiation xerostomia (74%) wanted to continue using the substitute than did patients with Sjögren's syndrome (44%). One-third of the patients did not wish to continue using either product. The authors felt that the most useful indices of effectiveness were night-time discomfort and difficulty in talking.

In a study of the viscosity of saliva and saliva substitutes, Levine and colleagues (*6*) showed that all but one of the artificial salivas tested (both carboxymethylcellulose and mucin-based) were more viscous than human parotid saliva and human submandibular saliva; the exception was Salivart. Laboratory studies have suggested that some artificial salivas have the capacity to induce rehardening of enamel, and Vissink and co-workers (*12*) suggested that this may be due to its being composed of carboxymethylcellulose, mucin, and sorbitol in certain proportions. One study by Weerkamp and others (*13*) of patients with Sjögren's syndrome, postradiation xerostomia, or chronic xerostomia suggested that a mucin-based product was more effective in restoring normal oral flora. This and several other studies also suggested that intraoral devices are useful in providing sustained release of these artificial salivas.

Several drugs, including bromhexine, anethole-trithione, and pilocarpine hydrochloride (*14*), have been assessed for their effectiveness as sialogogues in clinical trials. Other drugs that have been reported anecdotally to have this property include bethanecol hydrochloride, potassium iodide, neostigmine, and reserpine (*15*). Bromhexine is used in the management of chronic bronchitis, as it decreases the viscosity and increases the quantity of secretions. However, several studies of patients with Sjögren's syndrome have failed to show any improvement in salivary flow (*16,17*). No studies have been performed on patients with radiation-induced xerostomia.

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Anethole-trithione (Sialor, Sulfarlem) was reported as being used for the treatment of dry mouth following administration of some psychotropic drugs (*18*). The drug is thought to act by direct cell stimulation. A recent study by Ukai et al. (*19*) showed that chronic use in rats increased both salivary secretion and the number of muscarinic acetylcholine receptors. However, in a study in 1985 by Isaacson and Singer (*20*) that examined whole-body distribution of the drug in rats, there was no evidence of its presence in salivary glands. Several recent studies have examined the effectiveness of this drug in the treatment of chronic xerostomia, but reports differ as to its efficacy. Some studies found improvements in salivary flow, while others did not. The trial of DeBuck and colleagues (*18*) on patients with drug-induced xerostomia reported symptomatic improvement, and in the study by Epstein and colleagues (*21*), 74% of patients with Sjögren's syndrome had improvement in unstimulated whole salivary flow. However, studies by Schiødt et al. (*22*) and Malmstrom et al. (*23*), also on patients with Sjögren's syndrome, showed no improvement in salivary flow. The study by Hassenstein and co-workers (*24*) on patients with radiation xerostomia showed similar relief between the active group and controls (22% in the active group and 25% in the controls).

The cholinergic drug pilocarpine has been found effective in relieving symptoms and improving salivary flow in several studies. It appears to act by direct cell stimulation rather than by disturbing the cholinesterase-acetylcholine relationship (*25*). Saunte (*26*) found that giving pilocarpine subcutaneously to healthy volunteers caused an increase in whole salivary flow. Fox and colleagues (*27*) treated a group of patients with Sjögren's syndrome or chronic xerostomia for 2 days with active drug and for 2 days with placebo. In a more recent study, Fox and co-workers (*28*) treated additional patients with radiation-induced xerostomia, chronic xerostomia, or Sjögren's syndrome for 6 months with active drug, including 1 month with placebo. Salivary flow was improved in all patients in the first study and in 65% overall in the second study; symptomatic relief was reported by all the patients in both studies. Greenspan and Daniels (*29*) reported on the effect of pilocarpine in a 6-month double-blinded study. Patients who had received between 5,000 and 8,000 rads of external radiation were randomly assigned to be treated with pilocarpine or placebo. Each preparation was used for 90 days, and then the patient was crossed over to the other preparation for another 90-day period. Patients received 5.0–7.5 mg three to four times a day; the dose was based on symptoms and the patient's weight and was reduced for patients who experienced side effects. In this study, the test drug was discontinued 24 hours prior to measurement to eliminate the influence of direct drug effects. Salivary function was assessed by measuring stimulated whole salivary flow and parotid flow and by subjective evaluation. During the period on pilocarpine the subjects showed a measurable increase in parotid flow, but when on placebo their parotid flow was low. Some subjects taking placebo started their period on that preparation with a higher flow rate than at baseline because they had been taking pilocarpine for the previous 90 days. Results for whole flow rate were similar but less striking. When the effects of pilocarpine and placebo were compared, five of the 12 patients showed improvement by all three criteria, four showed improvement by two, and one patient showed no improvement. Nine of 12 reported symptomatic improvement while on pilocarpine, but when on placebo 10 of 12 showed no improvement.

Epstein and Schubert (*30*) examined the effectiveness of combining anethole-trithione (Sialor) and pilocarpine in the treatment of radiation xerostomia in patients who had not responded to other therapies. This was an uncontrolled, nonblinded trial. The patients were given Sialor, and 1 week later a 1% solution of pilocarpine was added. Salivary function was assessed by measurement of unstimulated whole flow and stimulated whole flow. Seven of nine patients noted symptomatic relief, and there was a statistically significant improvement in both unstimulated and stimulated whole-flow rates. The results of this trial suggested that this combination of drugs may be useful.

There is a need to study and develop more effective regimens for this patient population. Current therapies are directed towards empirical relief of symptoms or attempts to improve salivary flow. Future directions for study and research on saliva substitutes could include improvement in the viscosity and lubrication qualities of the constituents, development of constituents to deal with specific problems such as caries and candidiasis, and creation of better delivery systems to maintain a constant flow of artificial saliva.

Efforts to improve salivary gland function should aim at the development of better agents for the preservation of existing functional salivary gland and the development and testing of radioprotective agents (*31*). However, without standardized approaches to studies of salivary substitutes and stimulants, agents cannot be accurately compared. Investigators have used different criteria to evaluate symptomatic relief. Some studies measure whole salivary flow rates and some measure parotid flow rates. Some flow rates are stimulated; others are unstimulated. Researchers need to decide what the best criteria are for objectively and subjectively evaluating sialogogues and saliva substitutes in this patient population. Radiation-induced xerostomia is a common and troublesome condition. Patients need more effective treatments than are available today.

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Implications of Cancer Therapy to the Head and Neck on Growth and Development and Other Delayed Effects[1]

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Advances in the treatment of childhood cancers have resulted in a 50% decrease in death rates in the 1980s compared with those observed prior to 1965 (*1*). These treatment advances have included the use of multiagent chemotherapy given either alone or in combination with localized radiotherapy. The use of prophylactic cranial irradiation for patients with acute lymphoblastic leukemia (ALL) has decreased central nervous system (CNS) relapses and significantly contributed to improved survival. Patients with Hodgkin's or non-Hodgkin's lymphoma may receive upper-mantle irradiation, which includes irradiation to the neck. Patients with soft tissue sarcomas of the nasopharynx or brain tumors nearly always receive high-dose irradiation to the tumor site. Leukemia, lymphoma, and CNS tumors represent 70% of all childhood malignancies, and approximately 50%–60% of these children have their malignancy permanently eradicated with this "conventional" approach (*1–3*). The acute side effects of these treatments are numerous.

Advances in immunobiology, histocompatibility testing, immunosuppressive preparative regimens, and supportive care have led to the incorporation of marrow transplantation into the management of an ever-increasing number of patients with malignant and nonmalignant hematologic disorders (*4*). For some patients with hematologic malignancies or lymphomas, marrow transplantation offers improved disease-free survival compared to conventional therapy and represents the only possible cure for patients who have failed on conventional treatment (*5*). As the use of autologous marrow increases and the pool of suitable marrow donors expands to include related and unrelated individuals who are partially or fully HLA matched with the recipient, the ability to use this procedure for an even larger number of patients will increase.

Marrow transplant-preparative regimens are designed to suppress the patient's immune system to ensure engraftment and to eradicate the underlying hematologic disorder or malignancy (*6,7*). The agents used usually include high-dose cyclophosphamide (CY) given alone or in combination with other chemotherapy agents, such as busulfan (BU), or with total-body irradiation (TBI). Since all patients receive an infusion of marrow, doses are not limited by marrow toxicity.

The agents used in conventional treatment and for marrow transplant preparation have delayed effects that may affect the growth and development of young children. This report will review those that have been observed when cancer therapy is administered to or includes the head and neck.

NEUROENDOCRINE FUNCTION

When only chemotherapy is administered to children, adverse effects on growth and development have not usually been observed. However, when irradiation has been given as part of the conventional therapy or as part of a marrow transplant-preparative regimen, growth and development have been affected.

Thyroid Function

Little is known about the effects of conventional chemotherapy on thyroid function, but thyroid function abnormalities have been noted when therapeutic head and neck irradiation has been given to children with Hodgkin's disease, ALL, non-Hodgkin's lymphoma, nasopharyngeal sarcoma, and brain tumors. These children developed compensated hypothyroidism, overt hypothyroidism, thyroiditis, and thyroid neoplasms (*8–10*). Thyroid dysfunction usually began as asymptomatic compensated hypothyroidism within the first year after irradiation in 31%–53% of children and progressed to overt hypothyroidism in 25% over the next 5–10 years. Hypothyroidism is known to contribute to diminished linear growth.

Following marrow transplantation, thyroid function abnormalities were noted in one of 150 children who received chemotherapy-only preparative regimens with CY or BU plus CY (*11,12*). This incidence of less than 1% is not different than would be expected to occur in normal school-age children, and thus the chemotherapy given for marrow transplantation does not contribute to the occurrence of thyroid dysfunction. Marrow transplant-preparative regimens that include TBI, however, have been associated with thyroid dysfunction in 12%–56% of children (*13–15*). The highest incidence has been observed among patients who received 10.0 Gy of single-exposure TBI, with 28%–56% developing compensated hypothyroidism and 13% developing overt hypothyroidism. Patients who received fractionated-exposure TBI of 12.0–15.75 Gy have lower incidences of abnormal thyroid function, with 12%–21% developing compensated hypothyroidism and 3% developing overt hypothyroidism. These apparent differences in incidence most likely reflect the shorter observation times (median, 4–5 yr) after fractionated TBI schedules compared to the longer observation times (median, 8–9 yr) after single-exposure TBI.

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All children who receive irradiation to the neck, whether localized or as TBI, should be carefully followed for many years for development of abnormal thyroid function. For the majority of these patients, clinical manifestations are subtle or absent, and the diagnosis can best be established by measurement of thyroid-stimulating hormone (TSH) and thyroxine (T4) levels. Patients with compensated hypothyroidism (i.e., with elevated TSH) should be placed on thyroid hormone supplementation.

Growth Hormone and Growth Velocity

In general, children surviving long term after leukemia treatment that did not include cranial irradiation have normal or nearly normal growth rates (*16*). CNS irradiation has been associated with growth hormone (GH) deficiency and GH-releasing factor deficiency (*17–19*). The incidence of these deficiencies appears to be related to the child's age at the time of irradiation and the total irradiation dose given (*19–20*). A dose of more than 30.0 Gy to the pituitary has been estimated to be the threshold for impairment of GH production. Among children who received 18.0–24.0 Gy of cranial irradiation, results of GH production tests differ, which may be due to the use of various GH stimuli, the presence of a GH-releasing factor deficiency, or various time intervals between irradiation and GH determinations (*21,22*). Among these patients, both normal and subnormal growth rates and inconsistent responses to treatment with GH have been noted.

Irradiation to growing bones produces epiphyseal, metaphyseal, and diaphyseal injury that affects bone growth (*23,24*). The degree of the effect is related to patient age, site irradiated, total dose given, and dose schedule. The severity of the effect appears to increase with increasing irradiation dose, lengthening postirradiation interval, and younger age at time of treatment. Irradiation doses of 15.0–44.0 Gy to the entire spine result in suppression of spinal growth and decreased sitting height.

Children who have received 18.0–65.0 Gy of maxillofacial irradiation for lymphoma, leukemia, rhabdomyosarcoma, and other tumors have dental developmental abnormalities and altered growth of the facial skeleton (*25,26*). These problems have been observed in up to 82% of children evaluated 2–24 years after therapy. Dental abnormalities observed include foreshortening and blunting of roots, incomplete calcification, premature closure of the apices, delayed or arrested tooth development, and caries. Maxillofacial abnormalities included trismus, abnormal occlusal relationships, bimaxillary micrognathia, and hypoplastic mandible. The most severe abnormalities were observed in younger children receiving higher irradiation doses. Among marrow transplant patients given 10.0 Gy of TBI, similar disturbances in dental development and facial growth have been seen (*27,28*). Children less than 6 years of age all had arrested root development, premature apical closure, enamel hypoplasia, and microdontia. Those who were 7–12 years of age at the time of TBI usually only had arrested root development, with short, V-shaped roots. Vertical development of the lower third of the face, which is associated with alveolar bone growth and tooth eruption, was the most severely affected area of facial growth.

After marrow transplant-preparative regimens of CY only, longitudinal and growth velocity rates have been found to be normal (*29*). Decreased growth rates occur in nearly all children who receive regimens with TBI and 55% have subnormal GH production (*11,13*). GH deficiency was present in 87% of patients who had received cranial irradiation and in 42% who had not. During the first 2 years after TBI, patients with chronic graft-versus-host disease (GVHD) grew less well than those without chronic GVHD. After the first 2 years, growth rates were similar among all patients, and catch-up growth was not observed after treatment for chronic GVHD was stopped. This failure to achieve catch-up growth suggests that the effect of TBI on long bones may also contribute to these patients' decreased growth rates. Treatment with GH has led to modest improvements in height, but the growth rate has been less than usually observed in nonirradiated GH-deficient children.

Children who have received radiation therapy to the head and neck must be carefully followed for the impact on bone growth. If localized radiation has been given, facial structures may grow asymmetrically, but if whole-brain irradiation or TBI has been administered, growth will be symmetrical. In all instances, special attention to the development of secondary teeth is important. Children who are GH deficient derive an overall height benefit from GH therapy, but the impact of this treatment on the growth of facial structures and secondary teeth has not been studied.

OPHTHALMOLOGIC ABNORMALITIES

Cataracts are a well-known complication of exposure to long-term steroid therapy as well as to ionizing irradiation. Posterior subcapsular cataracts occurred in 80% of patients given a single exposure of 10.0 Gy of TBI by 6 years, and nearly all required cataract repair (*30*). Among patients given fractionated exposure of 10.0–15.75 Gy of TBI, 20 developed cataracts by 5 years, and of these, 20% required cataract repair.

Another late effect of irradiation to the eye is decreased lacrimal gland function with decreased tear formation (*31*). These patients have abnormal Schirmer's test results and may develop keratoconjunctivitis sicca and have corneal stippling on slit-lamp examination. Treatment with artificial tears or other ocular lubricants is necessary to prevent corneal ulcerations.

CENTRAL NERVOUS SYSTEM ABNORMALITIES

Intrathecal (IT) medications or cranial irradiation is given to nearly all children with ALL as prophylaxis or for treatment of CNS leukemia (*2*). Following this therapy, CNS structural changes and functional abnormalities have been noted (*32*). The actual incidence of long-term neurologic sequelae in patients treated with IT chemotherapy and cranial irradiation has not been determined, but when cranial irradiation was followed by weekly intravenous methotrexate at doses of 40 mg/m^2 or higher, over 50% of the children developed severe, irreversible leukoencephalopathy. Structural CNS changes such as ventricular dilatation, calcifications, and focal white matter hypodensity have been present on cranial computed tomography (CT) scans. Longitudinal studies have demonstrated that mild ventricular dilatation and white matter hypodensity may be reversible. The actual significance of these structural abnormalities has not been clearly defined, but ventricular dilatation has been correlated with verbal fluency defects, hypothalamic-pituitary dysfunction, and memory loss (*33*).

Multifocal leukoencephalopathy has been observed after marrow transplant-preparative regimens with TBI. One study of 415 patients receiving transplants for acute leukemia reported a 7% probability of developing leukoencephalopathy after TBI

and pretransplant IT medication (*34*). The major risk factor was pretransplant CNS treatment. The presence or absence of structural changes preceding and following TBI has not been studied.

Neuropsychological deficits have been reported for children surviving treatment for ALL (*32–36*). The bulk of evidence implicates CNS irradiation as the most likely agent contributing to these abnormalities (*35–37*). The age of the child at the time of treatment and the length of time after treatment also appear to be important (*38,39*). Children who were less than 8 years of age at the time of irradiation had lower IQ scores than children who received identical treatment at a later age. In addition, they performed less well with visual-motor, fine-motor, abstract thinking, and spatial-processing tasks (*40*). Thus, it may be anticipated that children who receive marrow transplants after TBI-containing regimens will be at risk for development of some neuropsychologic deficits. To date, no studies have been reported on this population of patients, but prospective evaluations are in progress.

Children who have received whole brain-irradiation should be carefully observed for development of neurological and neuropsychological difficulties. Early recognition of attention deficits and learning disabilities is necessary in order to facilitate referral for complete diagnostic evaluation, supportive treatment, and special-education classes.

SECONDARY MALIGNANCIES

Multiagent chemotherapy and irradiation have both been implicated as causes in the development of second neoplasms after treatment for childhood cancer. Among survivors of childhood ALL, 60 hematopoietic tumors and 51 solid tumors have been described (*32*). The median time from diagnosis of primary malignancy to development of the secondary hematopoietic malignancy was 22 months, and secondary solid tumors appeared between 5 and 15 years (median, 6). Of these solid tumors, 70% occurred in the head and neck, and in the majority of these cases the patients had received cranial irradiation. These second malignancies included brain tumors and carcinomas of the thyroid and parotid glands.

The time period of risk for development of secondary malignancies after radiation to the head or neck appears to be at least up to 40 years after irradiation (*9,10,41–43*). Patients surviving childhood Hodgkin's disease who were treated with multiagent chemotherapy have a cumulative 5%–6% probability of developing acute nonlymphoblastic leukemia or bone sarcoma at 10 years from initiation of treatment and a 19% cumulative risk of developing any type of secondary malignancy by 15 years (*42*). Long-term follow-up studies of children given irradiation for enlarged tonsils and adenoids or tenia capitus have demonstrated an increased incidence of neural and salivary gland tumors (*41,43*). These studies demonstrated that the risk of developing second tumors was also related directly to the irradiation doses received and that doses as low as 1–2 Gy could significantly increase the risk of neural tumors.

Studies of irradiated and nonirradiated mice given hematopoietic transplants suggested that GVHD was a major contributing factor in the development of secondary lymphoid malignancies (*44,45*). Among dogs given TBI and marrow transplantation, the relative risk of developing a malignancy was five times higher than in nonirradiated controls (*46*). Secondary malignancies in humans have also been observed after marrow transplantation (*47–52*). Among more than 2,000 transplant recipients, 35 developed secondary malignancies between 1.5 months and 14 years after transplantation (*52*). Non-Hodgkin's lymphomas, usually associated with Epstein-Barr virus, developed in 16 patients, six patients developed leukemias of a different type than the original leukemia, and 13 developed solid tumors. These solid tumors included gliomas, carcinomas, and melanomas. The major factors associated with an increased risk of development of these malignancies were related to GVHD immunosuppression treatment and TBI.

Thus, all patients who have received irradiation to the head and neck of any type need to be carefully followed for development of secondary malignancies. Any abnormal or suspicious skin lesion, nodule, severe headache, or sudden onset of neurologic deficits should be noted and the patient should be referred for detailed evaluation.

SUMMARY

These studies of late effects related to cancer treatment to the head and neck demonstrate that these patients may develop a variety of abnormalities, the majority of which occur after irradiation. Once a child is "cured" of a primary malignant disorder, visits to oncologists usually continue but decrease in frequency. Regular visits to the dentist continue and are usually at least a biannual event. Attention to the details of the patient's previous medical history is of paramount importance if the delayed effects discussed here are to be suspected and recognized. Early diagnosis of thyroid and GH deficiencies and institution of appropriate hormone treatment may improve these children's growth and development. Recognition of cataracts and dry-eye syndrome is important to prevent visual difficulties. Careful oral examination and attention to the patient's general overall neurological presentation is an important adjunct to diagnosis of learning difficulties and early recognition of second tumors of the head and neck.

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Mucosal Alterations[1]

Christopher A. Squier[2,*]

The initial effect of anticancer therapy, such as radiation and chemotherapy, is on the rapidly proliferating cells of the oral epithelium. As a consequence, the epithelium may show atrophy and ulceration. The sites of these alterations are related to the rate of epithelial proliferation. Regions of rapid proliferation, such as the oral lining mucosa, show a greater frequency of ulceration than masticatory mucosa or skin. Subsequent changes in the mucosa reflect damage to connective tissue, including fibroblasts and blood vessels. This results in hyalinization of collagen, hypovascularity, and ischemia. Indirect effects of anticancer therapy may include granulocytopenia and reduced salivary secretion, so that the protective mucin coating of the epithelium is compromised. These changes result in tissue with reduced barrier function and impaired ability to heal and to resist entry of pathogens, thus increasing the risk of systemic infections. [NCI Monogr 9:169–172, 1990]

The primary function of the oral mucosa lining the oral cavity, like that of the skin covering the surface of the body, is to protect the deeper organs and tissues. In all regions, the surface of the mucosa is covered with an epithelium that fulfills a barrier function by differentiation or maturation to produce a surface layer with adequate properties to meet functional demands put upon it, and by constantly replacing cells desquamated at the surface by divisions in the deeper, germinative epithelial layers (fig. 1). This process of constant epithelial renewal renders the oral mucosa very vulnerable to the effects of anticancer agents, for anticancer agents are selected for their action on proliferating cells. Once the continuity of the epithelial barrier is inadvertently disrupted by radiation or chemotherapy, there is an opportunity for a cycle of infection, inflammation, and tissue destruction to ensue that results in a painful and debilitating mucositis.

Ionizing radiation, primarily as a result of the generation of free radicals, brings about changes in DNA, damages proteins, and causes peroxidation of lipids (*1*). Chemotherapeutic agents may be alkylating agents that act directly on nucleic acids, antimetabolites that interfere with metabolic pathways leading to cell division, or antimitotic agents that disrupt structures in the cell needed to complete division (*2,3*). Experimental investigations of the effect of anticancer agents on oral mucosa are few, since ethical considerations limit the scope of human studies and there are few reports with animal models (*4–6*). However, it is apparent from existing studies that the major and immediate effect of anticancer agents is on the oral epithelium (fig. 2). This is a rapidly proliferating tissue with a turnover rate that is less than that of gut epithelium but greater than that of epidermis (*7*). However, there are marked regional differences in epithelial proliferation and turnover between different regions of the oral cavity (*8*). Although there are no consistent regional data on turnover or proliferation in human oral epithelia, results from studies on other primates indicate the differences that might be anticipated. Thus, rates in some of the lining tissues may be 1.5–5 times greater than in masticatory regions, such as palate or attached gingiva (table 1) (*9*). These differences are reflected clinically in the more rapid appearance of radiation-induced mucositis than of radiation-induced dermatitis (*10*) and in the prevalence of ulceration on nonkeratinized rather than keratinized mucosal surfaces (*11*).

Ulceration represents the breakdown of the epithelial continuity as a result of acute damage to the proliferating cell compartment so that desquamation at the surface is no longer matched by division. The basement membrane region may also break down and blisters may form, so that the complete epithelium is lost (*12,13*). However, if there is a cessation of therapy so as to permit repair and regeneration, the rapid proliferative ability of the oral epithelium permits healing in 2–3 weeks.

It is now known that not all cells in the epidermis or oral epithelium divide regularly. A small fraction of cells divide more slowly than others and seem to be capable of dividing indefinitely. These cells represent stem cells and may be important in repopulating the epithelium after damage from radiation or chemotherapy (*14*). Epithelial proliferation and differentiation may be controlled by a variety of factors, including epidermal growth factor, transforming growth factor β, and the interferons. It is also of interest that human trials with recombinant granulocyte colony-stimulating factor seem to bring about improved epithelial integrity (*15*). A better understanding of the effects of these factors could be important in preventing epithelial ulceration or promoting its healing.

Once the integrity of the epithelial barrier is compromised, the underlying tissues are exposed to the large and varied population of microorganisms resident in the oral cavity. This not only exacerbates the local mucosal lesion but predisposes the individual to systemic infections, particularly since there are indirect effects (fig. 3), such as leukopenia and neutropenia, following the administration of chemotherapeutic agents (*11*) and after myeloablative radiation therapy. Damage to the major and minor salivary glands not only lowers the oral levels of antibodies and antibacterial substances secreted in saliva but may also limit the benefits of the large salivary glycoproteins that bind to the surface of the oral mucosa. These glycoproteins are believed to contribute to the barrier properties of the

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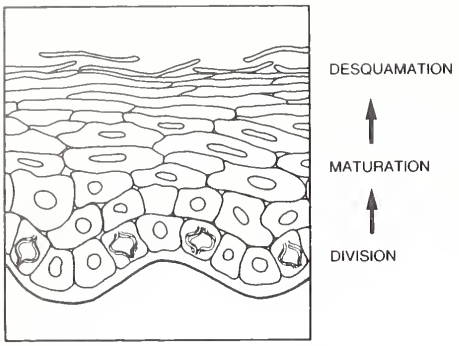

FIGURE 1. Diagram of oral epithelium as a constantly renewing tissue.

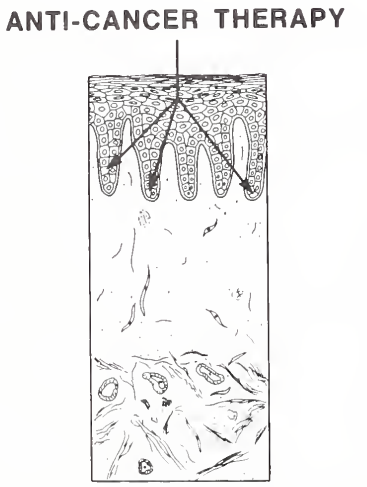

FIGURE 2. Anticancer agents affect the dividing cells in the deeper layers of the oral epithelium.

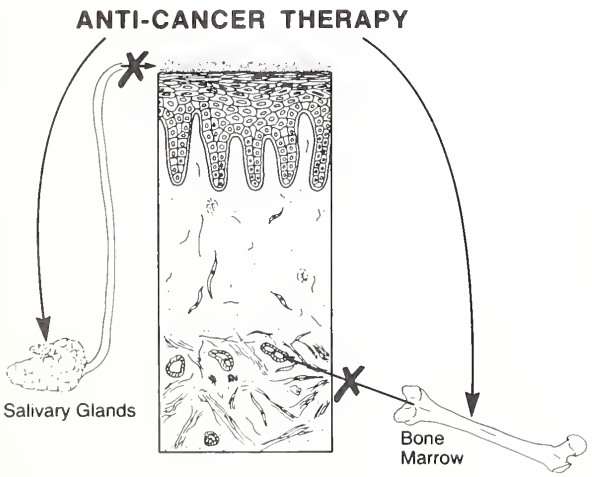

FIGURE 3. Indirect mucosal effects of anticancer therapy arise from damage to bone marrow and salivary glands, which can result in leukopenia, neutropenia, and reduced salivary mucin secretion.

Table 1. Epithelial cell proliferation in different oral regions in the tamarin monkey[a]

Tissue	No. of dividing cells/mm^2 of epithelial surface ($\bar{x} \pm$ SEM)
Soft palate	1.34 ± 0.18
Ventral surface of tongue	1.19 ± 0.10
Buccal mucosa	0.88 ± 0.14
Oral gingiva	0.79 ± 0.34
Hard palate	0.27 ± 0.05
Skin	0.13 ± 0.01

[a] Adapted from Rowat and Squier (*9*).

superficial cells by reducing adhesion of microorganisms and complexing with antigens (*16*). The absence of this glycoprotein coating may also render the surface epithelial cells more vulnerable to damage as a result of the therapeutic use of topical chlorhexidine, which is believed to bind to membrane proteins and thus disrupt cellular integrity (*17*). The mucin glycoproteins have now been precisely characterized, and it is important to consider introducing them into artificial saliva formulations.

The effects of cancer therapeutic agents on the connective tissue component of the mucosa (fig. 4) must be interpreted in terms of the lower rate of cell proliferation and turnover in this tissue. Ionizing radiation has a direct effect on the large molecules making up the ground substance so that depolymerization occurs, vascular permeability increases, tissue edema results, and inflammatory infiltrate is present (*18*). These changes are reflected in the acute erythematous clinical appearance of the mucosa seen after initial chemotherapy or radiation therapy. Both types of therapy affect the interphase cells in the connective tissue so that they may fail to divide normally, die after division, or become functionally or metabolically incapacitated. There are no studies of long-term changes in human oral mucosa after chemotherapy, although collagen loss has been

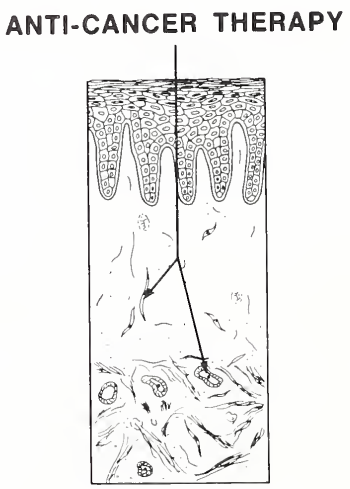

FIGURE 4. Effects of anticancer therapy on the connective tissue involve damage to cells, such as fibroblasts, and vascular changes.

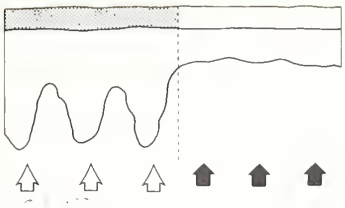

FIGURE 5. Connective tissue has a role in maintaining differentiation of the underlying epithelia. Nonkeratinized epithelium (stippled surface) may reflect a different connective tissue stimulus (open arrows) than that (solid arrows) responsible for the differentiation of keratinized epithelium (unshaded surface).

reported in the short term (up to 3 wk) in humans (*13*) and animals (*4*).

After radiation therapy, the connective tissue shows cell loss, appearance of abnormal cells, particularly fibroblasts, and development of fibrosis after about 6 months (*1,11*). Similarly, there are vascular changes involving occlusion of capillaries and narrowing of arteriole lumina as a result of endothelial swelling and fibrosis of the intima. This leads to hypovascularity and tissue ischemia (*1,18*). Together, these changes will reduce the ability of the tissue to heal when damaged and to resist infection.

One of the potential consequences of damage to the mucosal connective tissue is the effect it may have on maintenance of the overlying epithelium. It is now believed that the lamina propria has a major role in maintaining the appropriate pattern of differentiation of the oral epithelium (fig. 5) (*19,20*). In the 2–3 weeks following chemotherapy, the oral epithelium can show a variety of patterns of differentiation, but most changes are represented by hyperplasia and parakeratosis (*13,21*). These changes probably represent the proliferative epithelial reaction that is frequently seen after various types of clinical and physical trauma. In the longer term, after radiation therapy, there is often a shift in the pattern of epithelial differentiation towards a more atrophic tissue, which may reflect chronic changes in the lamina propria that affect the maintenance of normal maturation.

The severity and the rate of healing of the mucosal lesion seen after anticancer therapy depend on the age of the patient (*11*); older individuals are likely to recover more slowly from ulcerative damage. Clinically, in normal individuals, the oral mucosa tends to become atrophic, dry, and smooth with age (*22*), but there is little information available to explain these changes at a tissue level (*23*). There is probably a reduction in the rate of epithelial migration rather than cell proliferation with age (*8*), and this may explain the slow rate of healing after damage in the elderly.

A better understanding of the events following irradiation has permitted the development of fractionation schedules that permit healing and recovery from sublethal damage. The ability of mucosa to recover is similar to that of skin but less than that of slowly proliferating tissues, such as neural tissue (*6*). Hyperbaric oxygen treatment or augmentation of natural free-radical scavengers also offer encouraging prospects for improving the effectiveness of radiation therapy. However, much of our information on the mucosal effects of anticancer therapies is descriptive and does not provide insight into mechanisms. This insight is necessary if we are to develop agents with greater specificity that will limit unwanted damage or offer more than symptomatic treatment for the mucosal lesions that arise from existing therapies.

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Chronic Dental Complications

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Radiation therapy (RT) and chemotherapy have increased long-term survival with certain cancers. The use of dental investigation and treatment of chronic or delayed oral complications is developing. Altered dental root development, enamel opacities, hypocalcifications, periodontal problems, and a higher caries rate are seen in children treated with chemotherapy. The psychosocial implications of long-term survival on routine dental care are important. Prevention and treatment of long-term oral complications of radiation therapy are changing. Osteoradionecrosis remains complicated and devastating. Strategies that avoid post-RT extractions include caries prevention, oral hygiene measures, meticulous restorative dentistry, overdentures, and improved posts for endodontically treated teeth. Guidelines for post-RT extractions vary greatly. Pediatric patients who receive head and neck irradiation may have total arrest of tooth and jaw development within the portal. The dentist must be able to diagnose and treat the variety of alterations already identified and should engage in scholarly research to answer the questions that remain. [NCI Monogr 9:173–178, 1990]

Radiation therapy (RT) and chemotherapy have increased the long-term survival rate of patients with certain cancers. A new area of dental investigation and treatment of chronic or delayed oral complications is developing.

With regard to oral complications of chemotherapy, research has now identified a number of different expressions of altered dental root development in children treated with chemotherapy for cancer. From the last 10 years, 12 articles (*1–12*) were retrieved relevant to this subject; eight (*1–8*) focus on altered human tooth development with chemotherapy, while four (*9–12*) refer to chemotherapy effects on the human periodontium. In 1984, Jaffe et al. (*1*) described five of 23 patients treated with chemotherapy only (no radiation) who showed "acquired amelogenesis imperfecta," bicuspid microdontia, thinning of roots, and enlarged pulp chambers. Macleod et al. (*2*) histologically examined 21 teeth from nine patients on chemotherapy and reported increased prominence of the incremental lines within dentin. They related these changes to intravenous treatment or to the specific drug (vincristine), and their findings suggested a disturbance of microtubule function in odontoblasts, with decreased secretion of the collagen matrix.

Rosenberg et al. (*3*) performed both qualitative and quantitative analysis on 17 long-term survivors of acute lymphoblastic leukemia treated only with chemotherapy at between 4 and 10 years of age. All were studied after reaching age 12. Shortening, thinning, and blunting of roots and their apices were reported. Specifically, five of 17 had marked shortening and 13 of 17 had marked thinning of the root subjectively on periapical radiographs. From 63% to 84% of the premolars had quantitative radiographic shortening compared to the expected length with reference to the adjoining first molar. The impact on the quality of life, orthodontic treatment planning, periodontal therapy, and early mobility and exfoliation are described. The premolar-to-molar ratio analysis used is suggested as a research standard.

Enamel opacities, hypocalcifications, and a higher caries rate have also been noted in several studies (*4–7*), but it remains unclear whether these findings are due to direct alteration of enamel formation or maturation or to alterations in oral environment (saliva and flora), diet, and home care seen among patients who are on chemotherapy. Purdell-Lewis and others (*4*) in the Netherlands found more diseased and filled teeth in the 45 children treated with chemotherapy only. Some 43 of the 45 children showed disturbed amelogenesis with grooves, pits, and discoloration. Delayed eruption and shortened, malformed roots were also described. Pajari and others (*5*) in Finland described enamel opacities in all 37 children on chemotherapy only. The leukemia patients had opacities in all dentitions, while the other cancer patients showed alterations only of the permanent teeth.

Patients who received both chemotherapy and irradiation are described in two articles (*7,8*). Dahllof and others (*7*) in Sweden studied 16 bone marrow transplant (BMT) recipients who received chemotherapy and total-body irradiation. All 16 patients had impaired root development, with short V-shaped roots; five showed complete failure of root development with premature apex closure; and four had enamel hypoplasia. Fromm and others (*8*) reported on the late effects of treatment for 20 children with soft tissue sarcomas of the head and neck. Maleruption, caries, xerostomia, and craniofacial deformity were noted.

Wound-healing alterations have been reported for periodontal and oral surgical procedures done in chemotherapy patients and test-animal research studies. Van Story-Lewis et al. (*9*) showed one case of altered development in a patient on prednisone therapy for lupus erythematosus. In contradiction, Safkan and Knuuttila (*10*) studied 27 multiple sclerosis patients who had taken steroids for 1–4 years and compared them to age-matched multiple sclerosis patients not receiving steroids and to normal patients. They failed to find any changes in oral hygiene status, gingival condition, probing depth, gingival recession, or alveolar bone height. Wright (*11*) described periodontal tissue destruction and architectural defects in five cases of RT and chemotherapy. Seymour and others (*12*) studied the effects of azathioprine and cyclosporine on renal transplant patients and found gingival hyperplasia with increased probing depth on those patients receiving cyclosporine, which is also used with BMT recipients to prevent graft-versus-host disease.

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The literature has concentrated on the experimental model of giving chemotherapeutic agents to test animals and examining alterations in dental development. In experiments with rats, mice, and hamsters, the effects of cyclophosphamide, vinblastine, vincristine, doxorubicin, bleomycin, and 5-fluorouracil (5-FU) have been detailed (*13–63*).

Histological and histochemical changes are seen in the enamel, dentin, pulp, periodontal ligament, and Hertwig's root sheath. Altered enamel formation appears to be due to irregular enamel matrix formation, impaired secretory function, restricted membrane permeability of ameloblasts, decreased ameloblast reproduction, and inhibition of calcium exchange across the cell membrane to the enamel matrix. Calcium transport within the ameloblast was not apparently inhibited. These changes result in enamel opacities, surface irregularities, and the acquired amelogenesis imperfecta.

Dentinal changes appear to be due to impaired microtubule secretory function, which results in the formation of an irregular dentin matrix with unusual collagen aggregations. The polarity of odontoblast nuclei, as well as the number of cytoplasmic organelles, is lost. Increased intercellular spacing, reduced contact surfaces in desmosomes, and restricted membrane permeability are also observed. The clinical significance of these odontoblastic changes include shortening, thinning, and blunting of the tooth roots.

The pulp becomes hypocellular and thus prone to easier necrosis in the face of rampant caries. The destruction of Hertwig's root sheath (*16*) and the animal cell culture studies by Bellows et al. (*17*) of periodontal ligament collagen interaction with dentin support the findings of rootless teeth still having the capacity to erupt without complete root formation (*1–3,8*).

An additional area of investigation is the psychosocial implications of long-term survival on routine dental care. Best and Rosenberg (*64*) have noted that oncology patients have extensive interactions with a wide variety of medical-care modalities and personnel. The dental team must be sensitive to alterations of patient reactions to dental treatment. A number of different patient management techniques may be needed when delivering care to cancer patients.

The prevention, incidence, and treatment of long-term oral complications of radiation therapy are also changing (*65–102*). The xerostomia associated with head and neck irradiation has not yet yielded to chemodesensitizers as earlier research had promised. Little improvement has been made in the formulation of saliva substitutes. Fluoride therapy remains the mainstay of post-RT caries prevention. The role of long-term chlorhexidine therapy with RT patients is still uncertain.

Trismus is a serious problem that may be limited by early initiation of jaw-stretching exercises; treatment is usually ineffective in restoring a full range of jaw motions. Taste alterations, including ageusia, hypogeusia, and dysgeusia, may be permanent, and no effective treatment has been found; nutritional counseling may be an important component in managing patients with these disorders (*85–86*).

Osteoradionecrosis (ORN) remains the most complicated and devastating long-term post-RT complication. Its incidence appears to be related to dose, pre-RT dental condition, and the history of extractions immediately prior to, during, or at various intervals following RT (*87–102*).

Strategies of dental care that avoid post-RT extractions have emerged. Caries prevention through individualized oral care regimens, topical fluorides, frequent professional recall visits, and meticulous attention to the details of restorative dentistry are the foundation of long-term oral health maintenance.

Improvements of post design that reduce root fracture of endodontically treated teeth have come from bioengineering research (*107–111*) conducted to prevent the need to extract pulpally involved teeth in irradiated patients. If the root is fractured when a post is placed in it in order to build a substructure for retention of a prosthesis, the patient is put in a compromising position. The dentist cannot leave a fractured root because it will soon become infected and lead to ORN, nor can he remove the root because extraction in the irradiated patient may also lead to ORN of the mandible. Therefore, a post that is most likely to be retained (for success in restoration) and least likely to fracture the root is indicated.

Musikant, Deutsch, and others (*103,107–111*) have found that the chief causes of root fracture include the use of a tapered post that is overtorqued, "bottoming" and "topping" out, overpreparation of the post hole, failure to leave 1 mm of dentin intact, and excess pressure during cementation. The Flexi-Post system was designed to reduce fracture in the irradiated patient and has become widely accepted in a variety of applications for endodontically treated teeth (*103–111,114*). During the insertion, the split shank allows the threaded legs of the post to act as a collapsed tap. As the post is tapped into the root, it collapses, absorbing most of the stress that normally would be going into the root and possibly fracturing it (*107–112*). During loading (mastication), the Flexi-Post has been shown to cause fewer fractures of the root than even a passive post like the Parapost (*113*). The Flexi-Post is therefore recommended when the danger of root fracture is critical.

For periodontally involved or cariously nonrestorable teeth, the retention of roots (with or without endodontic therapy) and the use of overdentures seem preferable to extractions. McDermott and Rosenberg (*115*) described the factors involved in use of overdentures for the irradiated patient.

The guidelines for extractions in the RT patient vary greatly by treatment center and author (*87–102*). While no good data exist, the empiric use of careful surgical techniques, high-dose prophylactic antibiotics, and primary closure is advocated widely. The prophylactic use of hyperbaric oxygen (HBO) for prevention of ORN when extractions are needed in the irradiated jaws is advocated by Marx et al. (*92–95*) due to the high cost of treating ORN and the lower incidence of ORN in his series. The prophylactic use of HBO in this setting is refuted by Epstein and others (*88–90*), by Beumer and others (*97–102*), and by the clinical experience of other clinicians due to the low incidence of ORN induced by extractions compared to the cost of treating all extraction patients with HBO. The treatment of ORN also varies from center to center (*85–102*). It is my observation that the use of HBO seems to be related more to the reasonable access of a chamber to the patient and dentist than to the acknowledged treatment advantage of its use. New York City has only one HBO chamber, with no regular protocol to treat ORN. The University of California at Los Angeles has sent patients to Long Beach; M. D. Anderson Hospital in Houston has sent patients to San Antonio; and so on.

Pediatric patients who receive head and neck irradiation may have total arrest of tooth development at whatever stage the teeth have reached when RT is given (*1,5,7,8*). Some teeth form only part of the crown, some form just the crown without

forming roots, and others show only partial root development. The eruption of these arrested tooth aberrations despite cessation of root formation seems to refute the theories of tooth eruption that attribute Hertwig's root sheath and root formation as primary elements. Why these tooth aberrations erupt is currently unanswered. Altered growth of the jaws and facial bones in these pediatric oncology patients may lead to disfigurement and gross malocclusion. Maxillofacial prosthetic and/or orthognathic surgical treatment may become necessary.

The use of both chemotherapy and irradiation that includes the head and neck area has complicated the orderly research of long-term oral complications. The effects of this combined therapy are most evident in the patients who receive BMT, but such therapy is used also for certain Hodgkin's and non-Hodgkin's lymphomas, childhood leukemia (especially acute lymphocytic leukemia), pediatric sarcomas (embryonal rhabdomyosarcoma and osteogenic sarcoma), and neurologic malignancies (neuroblastoma, medulloblastoma, and gliomas). For these patients, the question arises whether the altered oral condition is due to the effects of the neoplasm, the chemotherapy, the radiation, or some combination which may act synergistically. Increased xerostomia-pattern caries and root sensitivity are often seen and may be due to salivary alterations and/or gingival hypertrophy and recession. In addition, malocclusion may be seen in these combination-therapy patients that may be due to altered eruption or to radiation- and/or chemotherapy-induced growth alterations, i.e., jaw and tooth size discrepancies.

The allogeneic BMT patient may also develop graft-versus-host disease (GVHD). Acute GVHD may cause a wide range of mild-to-severe long-term lichenoid reactions of the oral mucosa. Another primary target of GVHD is salivary gland tissue, with increased incidence of xerostomia and caries; daily topical fluoride therapy has proven effective with these patients, as it has with head and neck RT patients. Chronic GVHD is often associated with persistent oral ulcerations of immunologic and herpetic etiology and a scleroderma-like picture that causes trismus and associated problems of oral hygiene and access for dental care. The immunosuppressive drugs used to treat GVHD have a number of oral side effects, including increased oral herpetic and fungal infections as well as gingival hypertrophy in patients receiving long-term cyclosporine (*116–119*).

In summary, there are numerous chronic dental complications of RT and chemotherapy, whether used alone or combined to treat cancer. The dentist must be able to diagnose and treat the variety of alterations already identified and should engage in scholarly research to answer the questions that remain.

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Chemosensory Alterations and Cancer Therapies[1]

Linda M. Bartoshuk

Taste and olfaction provide sensory information and sensory pleasure. Cancer therapies affect both. Chemotherapy has not been shown to produce dramatic losses of taste or smell, but systematic studies on various chemotherapeutic agents and types of cancer are lacking. Radiation therapy does produce clear losses of both taste and smell. Both chemotherapy and radiation therapy alter the pleasure produced by taste and smell through the formation of conditioned aversions. That is, foods consumed in proximity with the nausea of therapy come to be unpleasant. The impact of conditioned aversions can be diminished by providing a scapegoat food just before therapy. Alterations in foods may be beneficial to the cancer patient. Increasing the concentrations of flavor ingredients can compensate for sensory losses, and providing pureed foods that retain the cognitive integrity of a meal can benefit the patient who has chewing or swallowing problems. [NCI Monogr 9:179–184, 1990]

We speak about "tasting" foods, but we actually taste, smell, and feel foods. When food is in the mouth, volatile compounds from the food rise from the mouth into the nasal cavity. Ultimately, the volatiles go through a small opening at the top of the nasal cavity called the olfactory pore. The olfactory receptors are inside the pore, which is located behind the eyes, just under the brain. We are not aware that olfactory sensations actually arise from this location because the brain does not record the location of the olfactory receptors.

Similarly, we are not aware of the exact location of the taste receptors. Taste receptor cells are gathered into globular clusters called taste buds. These are buried in the tissue of three types of taste papillae, the structures that can be seen on the tongue. Fungiform papillae can be seen on the tip of the tongue and on the front edges. Farther back, the parallel ridges on the rear edges are the foliate papillae. Across the rear of the tongue, the large, circular structures arranged in an inverted V are the circumvallate papillae. The papillae are located primarily on the edges of the tongue. The density of receptors diminishes toward the center of the tongue. When we taste, we are not aware of this distribution of receptors.

We fail to localize taste and smell sensations correctly because the brain uses the sense of touch to localize them (*1*). Because foods and beverages touch all over inside the mouth, their tastes and smells are localized there. We have probably come to use the verb "taste" to describe this experience because the taste receptors are genuinely in the mouth. We have a noun to describe the combination of taste and olfaction: flavor. However, we do not have a verb to express the act of perceiving flavor.

We can demonstrate the brain's failure to localize chemosensory sensations by creating some illusions. We have made taste appear to come from the center of the tongue by "painting" solutions from the tip of the tongue into the center with a Q-Tip (*2*). The touch of the Q-Tip pulled the taste sensation into the center of the tongue. Rozin (personal communication) demonstrated how odor is localized in the mouth by asking a subject to chew an odorless gum. Air from a reservoir of chocolate syrup was puffed into the mouth through a small tube. When the chocolate odor reached the olfactory receptors, the gum suddenly tasted like chocolate.

REGENERATION

In both taste and olfaction, receptor cells can be replaced. This has important implications for the recovery of the chemical senses from injury.

Taste

In taste, there is a synapse between the receptor cell and the sensory axon that carries taste input into the brain. The receptor cells have a normal life cycle of about 10 days (*3,4*). If damaged, the receptor cells can regenerate. The neurons connecting the receptor cells to the brain can also regenerate if damaged.

Recording studies show that a taste neuron's branches innervate receptor cells with similar taste sensitivities (*5*). This suggests that as receptor cells turn over, taste neurons are able to connect to a succession of similar receptor cell types in order to maintain their identities (e.g., as a neuron carrying "sweet" information). How this occurs is not known.

Olfaction

Olfactory receptors are not structures separate from the olfactory neurons. Rather, the olfactory receptors are the ciliated dendrites of the olfactory neurons. Since the olfactory neurons project into the central nervous system without synapses, there is a direct conduit from the olfactory receptor into the brain. If the olfactory system is damaged, it regenerates. The regeneration takes place from the olfactory cell up into the central nervous system (*6,7*).

PROCESSING OF TASTE AND OLFACTION

In taste, there are four qualities: sweet, salty, sour, and bitter. These are abstract terms that express intrinsic value (e.g., "she's sweet"). In olfaction, there are many qualities and no satisfactory classification system. The olfactory quality names are concrete; they identify the object that emits the odor (e.g., smoky, chocolate, minty, lemon).

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Since most substances in the real world are mixtures, the way in which the sensory systems process mixtures is particularly important. In the nineteenth century, mixtures were classified as analytic or synthetic. Auditory frequency provides an example of an analytic system. For example, if high, medium, and low notes are played on a piano, we hear all three frequencies. On the other hand, color mixtures are synthetic. When colors are mixed, the component colors are not perceived in the mixture.

In taste, mixtures are analytic. For example, in a mixture of sweet and sour, both sweetness and sourness can be perceived. In olfaction, mixtures can be perceived analytically (*8*). However, we can also process olfactory mixtures holistically (*9*). That is, we classify the mixture as a whole (e.g., pizza). Cain (*9*) has suggested that we store templates of many of these holistically processed olfactory mixtures in memory. We identify odors by comparing them to the templates. We are thus able to identify a large number of object odors.

AFFECT

The chemical senses of taste and olfaction provide important sensory information about the environment. However, they also provide affect: pleasure and displeasure. This affect seems like such an intrinsic part of the experience that many earlier experts believed that the affect of both taste and olfaction was "hard-wired" in the brain and required no experience. Modern research (*10*) supports this conclusion for taste. For example, newborns respond to sweet with facial expressions suggesting pleasure to adult observers ("slight smile," "eager licking of the upper lip") and to bitter with facial expressions suggesting displeasure ("preparatory movements of vomiting").

Olfaction

The affect of olfaction appears to be learned. At the age of 2 years, children still do not show the affective reactions to odors shown by adults [Lipsitt and Engen, cited in Engen (*11,12*)]. By the age of 3 years, olfactory affect begins to resemble that of adults (*13*).

The affect of olfaction is relatively labile. Simple exposure to an odor can change its pleasantness. For example, workers in factories with obnoxious odors get used to the odors and can even eat lunch in their surroundings (*14*). Pairing odorants with pleasurable experiences like the taste of sweet (*15*) or the presence of calories (*16*) increases the pleasantness of the odorant. Pairing odorants with nausea decreases their pleasantness (*17*). This pairing plays an important role in the development of food aversions during chemotherapy.

EFFECTS OF CANCER AND THERAPY

Taste and olfaction have both sensory and hedonic attributes. Thus, there are both sensory and hedonic disorders of taste and olfaction. The sensory disorders of the chemical senses include loss of function and the presence of phantom sensations. The phantom sensations are usually more disturbing than simple losses. Because of the negative affect, chronically present unpleasant tastes or smells are much like chronic pain.

Loss of taste and/or smell can produce hedonic loss because of the hedonic properties of taste and smell. However, the major hedonic disorder is the acquisition of conditioned aversions. This makes the consumption of particular foods distasteful to the patient.

Cancer Per Se

One of the myths that persists in this field is that cancer somehow alters the sensations of taste, leading patients to stop eating. Cancer patients often do have appetite problems. This is manifested by patient comments like "Food just doesn't taste good anymore." This may seem to suggest that the taste of food has somehow changed, but this is often a misunderstanding of the patient's experience. The patient's feelings about eating are more likely to be the source of the complaint. Careful questioning can elicit a more accurate description from the patient. For example, a patient seen at the Connecticut Chemosensory Clinical Research Center reported that she could not eat because food tasted bad to her. She was asked to eat one of the foods that she used to like (tuna salad) in the clinic. When asked what it tasted like, she replied, "Tuna salad." When asked in what way it differed from the way tuna salad used to taste, she replied that it did not differ at all but that it no longer tasted "good." She experienced a hedonic change, not a sensory change.

Perhaps the best known of the studies that searched for a sensory alteration was that of Dewys and Walters (*18*). This study reported elevated sucrose (sweet) thresholds and lowered urea (bitter) thresholds in some cancer patients. The authors noted that the elevated sucrose thresholds correlated with patient reports of reduced appetite. They suggested that the low thresholds for urea might reflect an increased taste of bitterness in meats (because of small amounts of bitter substances), leading to an aversion for meats.

This study was followed by other studies that reported some elevated taste thresholds (*19,20*); however, these studies did not confirm the low bitter thresholds reported by Dewys and Walters (*18*). The National Cancer Institute funded additional research [e.g., Settle et al. (*21*)] to resolve this issue. Settle et al. not only failed to replicate the results of Dewys and Walters, but more importantly questioned the statistics in the Dewys and Walters study (*18*). Dewys and Walters's conclusion that increased sensitivity to bitter produced meat aversions rested on their observation that eight of 50 cancer patients had unusually low urea thresholds while only one of 23 controls had a low urea threshold. They reported a chi-square of 10.5 ($P < .005$) for this difference. However, the correct chi-square for these data is 1.05, which is not statistically significant. There is no evidence for increased taste sensitivity to bitter in cancer.

Trant et al. (*22*) resolved many of the difficulties associated with the earlier studies. First, they evaluated perceived intensities rather than the thresholds of taste solutions. This is a more valid way to assess real-world taste function, since thresholds merely measure the lowest concentration that can be tasted and this does not necessarily predict how intense stronger concentrations taste (*23–26*). Trant et al. (*22*) found normal taste perception in cancer patients.

Chemotherapy

Chemotherapy and Sensory Loss

There is little evidence for taste or olfactory losses produced by chemotherapy. Trant et al. (*22*) looked at chemotherapy within their study and found normal taste in chemotherapy patients. Olfactory function vis-a-vis chemotherapy has received virtually no attention. More research is needed on this issue since the types of therapeutic agents and types of cancer

have not been systematically evaluated. With regard to taste, losses localized to specific regions should also be evaluated.

Since chemotherapy damages cells, one would expect both taste and smell to be vulnerable. Since both taste and smell can regenerate, potential losses should be evaluated across time. Tests comparing chemosensory function before and after therapy would be the most sensitive for measuring any damage that might occur.

Chemotherapy and Phantom Sensations

Bitter tastes. Several studies have noted that some patients report a bitter taste during chemotherapy (*27–29*). Many drugs taste bitter. The ability to perceive bitterness is believed to have evolved as a means of detecting poison. If this is the case, then the bitterness of medications is not hard to understand. Poisons and medications both tend to be organic substances that chemically interact with human physiology. In fact, many medications are derived from substances first discovered for their poisonous effects at higher concentrations.

Medications can be tasted (or smelled) when they make their way into the oral and nasal cavities. One obvious route is saliva. A variety of drugs, including some used for chemotherapy, are known to be passed into saliva (*30,31*). Another route is crevicular fluid (*32*). This fluid originates from blood plasma and can be expressed into the mouth during chewing.

Less likely but possible routes by which unwanted substances can enter the mouth and nasal cavity include diseased teeth, poor oral hygiene, bacterial infections, postnasal drip, stomach reflux, volatiles in exhaled air, and local infections in the nasal cavity.

The venous taste phenomenon offers another way in which medications can be tasted (*33,34*). This phenomenon was, at one time, used to measure circulation time (*35*). When a bolus of a tastable substance is injected into a vein, it can be tasted when the blood containing it reaches the taste buds. It is believed that the tastant diffuses from the blood to the bottoms of taste cells. We cannot rule out the possibility that the tastant is actually reaching the surface of the tongue, where it can be tasted in the normal way. However, the speed with which the taste occurs argues that we can taste substances directly from blood.

Bitter tastes from chemotherapy and genetic status for taste blindness. Fetting et al. (*27*) suggested that the taste of chemotherapeutic medications might be related to the genetic ability to taste phenylthiocarbamide (PTC).

The inability to taste PTC and close chemical relatives like 6-*n*-propylthiouracil (PROP) is believed to be a simple Mendelian recessive characteristic (*36*). To be a taster of PTC/PROP, one must carry at least one dominant gene. Some individuals who are exceptionally sensitive to PTC/PROP might carry two dominant genes.

Interviews with a series of patients undergoing chemotherapy at Yale-New Haven Hospital suggested a connection between the perception of a bitter taste during chemotherapy and the perception of bitterness in saccharin (Rifkin and Bartoshuk, unpublished observations). The bitter taste of saccharin is associated with genetic status for PTC/PROP tasting (*37*). We have seen two patients suffering from bitter tastes during chemotherapy who offer additional support for connection with PTC/PROP status. In one case, a female patient was distressed about the bitter taste that she experienced during chemotherapy. On interview she admitted that she thought that the taste meant her disease was progressing. Testing revealed that she was a very sensitive taster of PTC/PROP. We reassured her by explaining that her sensitivity to certain bitter tastes produced her symptom and that it had nothing to do with cancer. A second woman came to the Connecticut Chemosensory Clinical Research Center complaining of a bitter taste during chemotherapy that was so intense that she could not eat. Testing revealed that she too was a very sensitive taster of PTC/PROP. The possibility of a connection between PTC/PROP tasting and the bitter tastes associated with chemotherapy should be evaluated.

Smells perceived during chemotherapy. An odorant injected into the blood can be perceived, apparently because the odorant diffuses from nasal capillaries to the olfactory receptors (*38*). Thus if chemotherapeutic agents have odors, these may be perceived by patients.

Chemosensory sensations induced by thoughts associated with chemotherapy. Nesse et al. (*39*) reported patients' accounts of "pseudohallucinations" associated with chemotherapy. One woman experienced a "chemical odor" when she thought about her chemotherapy. This was the same chemical odor that she had noticed in the clinic and that made her nauseated. This woman was reluctant at first to talk about her experiences because she thought "maybe I was going bats."

Olfactory hallucinations have been associated with mental illness (*40*), and they occur in connection with epilepsy (*41*) and migraine headaches (*42–44*). However, they also occur in normal individuals who have been exposed to intensely emotional experiences. Burstein (*45*) reported two cases of posttraumatic stress disorder that involved olfactory hallucinations. A woman who had been in an automobile accident smelled gasoline while riding as a passenger in her husband's car; a man who had been in a fire reported flashbacks in which he experienced the smell of smoke just as he had in the fire.

Chemotherapy and Conditioned Aversions

Bernstein (*46*) was the first to suggest that the loss of appetite in cancer might be explained in part by the acquisition of conditioned aversions to foods and beverages through the nausea produced by chemotherapy. A classic picture of a conditioned aversion was given by Garb and Stunkard (*47*): "If a person becomes sick after eating a specific food, he may develop an intense dislike, called an 'aversion,' for that food, whether or not it was responsible for the illness." Conditioned aversions are common in the population (*47,48,72*). Pelchat and Rozin (*17*) showed that foods become "distasteful" when paired with nausea.

Bernstein (*46*) gave a novel ice cream flavor to children about to undergo chemotherapy. They developed an aversion to that flavor of ice cream, but the aversion was not shown by the controls. In a very dramatic follow-up to this research, Bernstein and colleagues (*49*) found that children who did not get ice cream before chemotherapy developed more aversions to foods in their normal diets. This suggested that the ice cream acted as a scapegoat for the experimental subjects. It was as if the ice cream "attracted" the aversion to itself and spared the diet. Bernstein has extended her original work to adults (*50*).

Other investigators have confirmed conditioned aversions in chemotherapy patients (*51–53*), and one study using normal

volunteers was done to shed light on some of the important issues in the conditioning of aversions (*54*).

Taste Versus Olfaction in Conditioned Aversions

Conditioned aversions have been studied extensively by learning theorists. In lower species, conditioned aversions appear to form more easily to taste than to olfaction. In humans, just the reverse is true. Conditioned aversions in everyday life form as a result of genuine cases of poisoning but more commonly form as the result of accidental pairings of foods with nausea from G.I. illness. One of the most common sources of conditioned aversions in young people is illness from consumption of alcohol (*48,72*). An analysis of the foods or beverages to which the aversion generalizes suggests that human subjects generalize either to the olfactory sensations or to cognitive properties of the food like its appearance or its container (Bartoshuk and Wolfe, unpublished observations).

Radiation Therapy

Ethna M. MacCarthy-Leventhal, a physician herself, wrote a poignant account in *The Lancet* of her experiences during treatment by radiation therapy for cancer of the pharynx (*55*). She described a "blindness of the mouth" that robbed food of its usual taste. In addition, she described a "hallucinatory" taste (bicarbonate of soda) that "haunts all liquids." Her essay conveys the great suffering that disturbances of taste and olfaction can cause.

A Russian study [Kuznetsova, 1960; cited in Kimeldorf and Hunt (*56*)] reported that 43% of a population of Betatron workers exposed for 4–10 years showed diminished taste and olfactory sensitivity. We now have additional observations of chemosensory disturbances from therapeutic radiation.

Radiation Therapy and Sensory Loss

Taste. A case of taste loss produced by radiation therapy for cancer on the left side of the rear of the tongue was described by Kalmus and colleagues (*57,58*). Kalmus was famous for devising a threshold method for the study of taste blindness to PTC. He used this method to evaluate the patient's recovery from taste loss. Recovery, as measured by return of thresholds to normal, took about 2 months. Two additional observations are worth noting. Early in the therapy, food was "nauseating," "greasy," or "rancid." Liquids tasted "metallic" or "salty." The time course of recovery of taste thresholds was confirmed by Conger (*59*) for nine patients.

Because these changes in taste were measured with thresholds, they have limited relevance for real-world taste. Both threshold and suprathreshold taste function were evaluated in a patient with cancer of the neck (*24*). The two measures led to dramatically different conclusions. The threshold measures returned to normal after the expected 2 months. However, the suprathreshold functions did not return to normal. Shortly after radiation therapy began, the patient lost the ability to taste both strong and weak tastes. After 2 months, she could recognize the four taste qualities, but when the concentration rose, the perceived intensities of the tastes did not rise. The patient lived in a pastel taste world.

Mossman and Henkin (*60*) observed the same dissociation between threshold and suprathreshold function. In a later paper with additional colleagues (*61*), they compared the effects on taste of conventional photon radiation and cyclotron-produced fast neutrons. They found no differences.

Olfaction. Genuine olfactory loss from radiation therapy has been recognized only recently. Doty (*62*) mentioned in a review on olfactory dysfunctions that he had seen a patient with anosmia following radiation treatment. After pituitary irradiation, one patient developed anosmia that persisted for 21 months (*63*). Among 12 patients with radiation to the olfactory mucosa, smell thresholds for two test odorants increased dramatically (*64*). Even 6 months after the treatment, none of the patients showed complete recovery. Olfactory loss deserves more attention.

Radiation Therapy and Phantom Sensations

In a book on ionizing radiation, Kimeldorf and Hunt (*56*) reviewed a series of papers suggesting that abnormal sensations result from early effects of radiation. Some of the effects described appear to result from the stimulation of sensory receptors by low-level radiation. However, others may have resulted from damage. Lindemann [cited in Kimeldorf and Hunt (*56*)] noted in 1949 that a common early effect of radiation of the oral cavity and the larynx was a metallic taste. A metallic taste also occurs in patients who have had chorda tympani nerve sections (*65*).

Radiation Therapy and Conditioned Aversions

Radiation therapy can produce nausea and therefore can produce conditioned food aversions. Smith et al. (*66*) were the first to demonstrate conditioned food aversions from radiation therapy. Carrel et al. (*67*) replicated the finding. Radiation to the abdomen was the most likely to produce nausea and conditioned aversions.

Anticipatory Nausea

Anticipatory nausea appears to be related to conditioned food aversions. The stimuli associated with chemotherapy (e.g., smell of the clinic, smell of a nurse's perfume, voice of the doctor) act as conditioned stimuli and come to evoke the unconditioned response, nausea and vomiting (*71*). In conditioned food aversions, the food is the stimulus that can evoke distaste or even nausea and vomiting. In lower species, food stimuli condition to nausea easier than other stimuli. This is presumably true with human subjects as well.

THERAPEUTIC INTERVENTIONS

Strategies to Deal With Learned Aversions

Broberg and Bernstein (*68*) provided candy to children before chemotherapy and successfully blocked the formation of conditioned aversions to foods.

Since animals form conditioned aversions best to novel stimuli, Andresen (*52*) studied the novelty of the conditioned stimuli as well as the exact time course of nausea and exposure to novel and familiar foods. She offered clinical recommendations on the basis of her studies. These include:

1. The patient should avoid novel foods that are nutritionally important in his/her diet prior to treatment and that are likely to lead to nausea and vomiting.

2. The patient should eat a novel food not important to the diet

about 10–15 minutes before chemotherapy. This becomes a scapegoat for the aversive conditioning.

3. Nutritionally important foods should not be consumed until the nausea completely ends.

4. Since nausea increases with the number of foods eaten before treatment, fasting for 4 hours before treatment may help reduce nausea.

5. A patient can attempt to extinguish the aversive conditioning by consuming conditioned foods at times when he/she feels well.

6. A patient should be educated about food aversions.

Changing the Food Instead of the Patient

Schiffman (*69*) increased the palatability of foods for the elderly by intensifying the odors to compensate for the fact that olfactory sensations diminish with age. Similarly, as we come to understand the effects of cancer therapies on the sensory and hedonic properties of the chemical senses, we will be able to alter foods for cancer patients.

Randy Breslin, Director of Food Services, Connecticut Hospice, has produced a pureed menu for cancer patients that maintains all of the sensory characteristics of normal meals except texture (*70*). Breslin's menus are prepared in two ways. One type of meal is provided for patients who can chew and swallow normally. The other type of meal is actually pureed, although its appearance is that of a normal meal. Breslin has accomplished this in a variety of ways. Among the most dramatic of her pureed items is a pork chop that consists of pureed meat reformed on the bone and glazed to look intact and a plate of cold cuts, ground, reformed into loafs with gelatin, sliced, and arranged to look like intact cold cuts.

Maintaining the cognitive integrity of the meal not only adds to the pleasure produced by the appearance of the meal, it might also contribute in an unsuspected way to sensory enjoyment in patients with sensory loss. At the Connecticut Chemosensory Clinical Research Center, interviews with anosmic patients reveal that some of them eat in expensive restaurants even though objective tests suggest that they would derive little sensory pleasure from doing so. To our surprise, some patients report pleasure from the experience that appears to go beyond the ambience. The appearance of the food and the surroundings appear to render the eating experience more like the patient remembers it. This cognitive contribution to the experience of eating deserves more attention.

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